

## ***Therapeutic Class Review Selective Serotonin Agonists***

### **Overview/Summary**

Migraine is a chronic neurovascular inherited disorder. Classical features of a migraine attack include a pulsating, throbbing headache that can last up to 24 hours; it is often accompanied by nausea, photophobia, lightheadedness, and vomiting. Migraine affects approximately 18% of women and 6% of men in the United States (US).<sup>1</sup> The introduction of the selective serotonin agonists, or triptans, was an important advancement for the treatment of migraine. Currently, 7 single-entity selective serotonin (5-hydroxytryptamine, or 5-HT<sub>1</sub>) receptor agonists and 1 combination product (Treximet<sup>®</sup>; sumatriptan/naproxen sodium) are available in the US.

Sumatriptan, the first of the triptans, was introduced in the US in 1993 as a subcutaneous (SC) dosage form that was followed by oral and intranasal formulations. Six second-generation 5-HT<sub>1</sub> agonists were later approved by the Food and Drug Administration (FDA): zolmitriptan (1997), naratriptan (1998), rizatriptan (1998), almotriptan (2001), frovatriptan (2001) and eletriptan (2002). The combination product sumatriptan/naproxen sodium was approved by the FDA in 2008. Currently, only sumatriptan is available generically.

The 5-HT<sub>1</sub> agonists are chemically and structurally related to the neurotransmitter 5-hydroxytryptamine, which is present in the blood and in the peripheral and central nervous systems.<sup>2</sup> These drugs are potent, highly selective 5-HT<sub>1</sub> receptor agonists, with no significant affinity for other 5-HT subgroups.

The 5-HT<sub>1</sub> receptor agonists stimulate the serotonin receptors located on cerebral vessels to redistribute blood flow and relieve pain. The result is a decrease in neurologic-mediated plasma protein leakage, and thus a decrease in hemicranial pain and vasodilation associated with neurogenic inflammation.<sup>3</sup>

### **Medications**

**Table 1. Medications Included Within Class Review**

| <b>Generic Name (Trade name)</b>                             | <b>Medication Class</b>      | <b>Generic Availability</b> |
|--|------------------------------|-----------------------------|
| <b>Single Entity Products</b>                                |                              |                             |
| Almotriptan (Axert <sup>®</sup> )                            | Selective Serotonin Agonists | -                           |
| Eletriptan (Relpax <sup>®</sup> )                            | Selective Serotonin Agonists | -                           |
| Frovatriptan (Frova <sup>®</sup> )                           | Selective Serotonin Agonists | -                           |
| Naratriptan (Amerge <sup>®</sup> )                           | Selective Serotonin Agonists | -                           |
| Rizatriptan (Maxalt <sup>®</sup> , Maxalt MLT <sup>®</sup> ) | Selective Serotonin Agonists | -                           |
| Sumatriptan (Imitrex <sup>®</sup> )                          | Selective Serotonin Agonists | ✓                           |
| Zolmitriptan (Zomig <sup>®</sup> , Zomig ZMT <sup>®</sup> )  | Selective Serotonin Agonists | -                           |
| <b>Combination Products</b>                                  |                              |                             |
| Sumatriptan/naproxen (Treximet <sup>®</sup> )                | Selective Serotonin Agonists | -                           |

**Indications****Table 2. Food and Drug Administration Approved Indications<sup>4-12</sup>**

| Generic Name          | Migraine, Acute, with or without Aura | Cluster Headache |
|-----------------------|---------------------------------------|------------------|
| Single Entity Product |                                       |                  |
| Almotriptan           | ✓                                     |                  |
| Eletriptan            | ✓                                     |                  |
| Frovatriptan          | ✓                                     |                  |
| Naratriptan           | ✓                                     |                  |
| Rizatriptan           | ✓                                     |                  |
| Sumatriptan           | ✓                                     | ✓ (subcutaneous) |
| Zolmitriptan          | ✓                                     |                  |
| Combination Product   |                                       |                  |
| Sumatriptan/naproxen  | ✓                                     |                  |

**Pharmacokinetics**

There are differences in the pharmacokinetic parameters of the selective serotonin agonists. Since the development of sumatriptan, alternative agents have been designed. In general, these new drugs, also known as second generation selective serotonin agonists, have higher bioavailability, and a longer plasma half-life. Sumatriptan, rizatriptan, and zolmitriptan have the most rapid onset of action. A longer half-life and increased brain penetration may prevent headache recurrences.<sup>13</sup>

**Table 3. Pharmacokinetics<sup>14</sup>**

| Generic Name          | Dose and Route of Administration | Onset (hours) | T <sub>max</sub> (hours) | Bio-availability (%) | Serum Half-Life (hours) | Plasma Protein Binding (%) |
|-----------------------|----------------------------------|---------------|--------------------------|----------------------|-------------------------|----------------------------|
| Single Entity Agents  |                                  |               |                          |                      |                         |                            |
| Almotriptan           | 12.5 mg PO                       | 0.5-2         | 2.5                      | 80                   | 3.1                     | 35                         |
|                       | 25 mg PO                         |               | 2.7                      | 69                   | 3.6                     |                            |
| Eletriptan            | 20 mg PO                         | 1             | 2                        | ≈50                  | ≈4                      | ≈85                        |
| Frovatriptan          | 2.5 mg PO                        | 2-3           | 3                        | 29.6                 | 25.7                    | ≈15                        |
|                       | 40 mg PO                         |               | 5                        | 17.5                 | 29.7                    |                            |
| Naratriptan           | 2.5 mg PO                        | 1-3           | 2                        | 74                   | 5.5                     | 28                         |
| Rizatriptan           | 10 mg PO                         | 0.5-2         | 1<br>(ODT: 1.6-2.5)      | 40                   | 2                       | 14                         |
| Sumatriptan           | 6 mg SC                          | 0.2           | 0.17                     | 96                   | 2                       | 14-21                      |
|                       | 100 mg PO                        | 0.5-1         | 1.5                      | 14                   | 2                       |                            |
|                       | 20 mg IN                         | 0.25-0.3      | 1.5                      | 15.8                 | 1.8                     |                            |
| Zolmitriptan          | 2.5 mg PO                        | 0.75          | 1.5<br>(ODT: 3)          | 39                   | 2.3/2.6 <sup>*</sup>    | ≈25                        |
|                       | 5 mg PO                          |               | 1.5<br>(ODT: 3)          | 46                   | 3                       |                            |
|                       | 5 mg IN                          | 0.25          | 3                        | 102 <sup>†</sup>     | ≈3                      |                            |
| Combination Products  |                                  |               |                          |                      |                         |                            |
| Sumatriptan /naproxen | 85 mg/500 mg PO                  | 1/5           | 1/5                      | 15/95                | 2/19                    | 14-21/99                   |

IN=intranasal, ODT=orally disintegrating tablet, PO=oral, SC=subcutaneous

\*Values for men and women, respectively.

†Compared with oral tablet.

### **Clinical Trials**

Clinical trials have demonstrated that 5-HT<sub>1</sub> receptor agonists are highly effective in treating and providing relief from migraine headache attacks with or without the presence of aura, cluster headaches and menstrual-related migraines. There is a plethora of clinical data that compares the efficacy and safety of the individual triptan products for the treatment and acute management of these headache disorders. National and international treatment guidelines recognize the efficacy and safety of acute treatment with triptans and note that all available agents are considered equally efficacious; giving no preferential status to one agent over another.

Numerous clinical trials have compared the triptans to placebo and to other agents in the same class.<sup>15-70</sup> The inclusion criteria of these studies were designed to create a study population that most closely mimics the general population that is affected by migraine headaches. The studies included adult patients with migraine headaches, and the general results of these trials have established the efficacy of these agents in the treatment of migraine with or without aura by improving patient reported signs and symptoms of migraine attacks; however, no particular agent overall has been found to be consistently more efficacious than another agent.

Sumatriptan/naproxen was significantly more effective in achieving headache pain relief measured by the reduction of moderate-severe pain intensity to mild intensity or no pain without the use of rescue medications compared to placebo in controlled trials. Sumatriptan/naproxen was also compared to each individual component separately and was shown to be significantly more effective in achieving headache pain relief; however there are no head-to-head trials comparing sumatriptan/naproxen to other triptans or to sumatriptan along with naproxen as separate therapies administered concurrently.<sup>66-70</sup>

Although limited in the number of clinical trials conducted, the use of triptans has been shown to be clinically efficacious in treating menstrual-related migraines.<sup>71-72</sup> Although not statistically significant, the use of almotriptan and zolmitriptan demonstrated a clinical response in 67.9% and 68.6% of the almotriptan and zolmitriptan-treated women after two hours from dosing. Recurrence rates within 24 hours of dosing were similar among the treatment groups, as was the sustained pain-free assessments among treated women. Frovatriptan was efficacious, proving to be better than placebo in treating menstrual-related migraine headaches. Twice daily dosing of frovatriptan was determined to be more efficacious than once-daily administration ( $P<0.0001$ ).

Sumatriptan administered subcutaneously (SQ) is the only product with a Food and Drug Administration (FDA)-labeled indication for managing cluster headaches. Sumatriptan administered SQ in a small clinical trial was reported as successful in 88% of all attacks.<sup>74</sup> A separate single-dose study illustrated the efficacy of sumatriptan 6 mg and 12 mg SQ vs placebo, with relief being reported in 75% and 80% of patients treated with 6 mg and 12 mg, respectively ( $P<0.001$ ); however the analysis between the two sumatriptan strengths was not statistically significant.<sup>75</sup> Additionally, frovatriptan has also been shown to have positive results in combating cluster headaches. In a small trial of episodic and chronic cluster headache sufferers, frovatriptan provided at least 75% improvement in 8 of 9 patients with episodic cluster headaches, and 100% migraine relief within 48 hours. Three of 8 patients with chronic cluster headaches were reported to have had complete relief by study endpoint.<sup>73</sup>

**Table 4. Clinical Trials**

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration | End Points  | Results   |
|---|---|--------------------------------|---|---|
| <b>Migraine With or Without Aura</b>  |   |                                |   |   |
| Cabarrocas et al <sup>15</sup><br><br>Almotriptan 12.5 mg   | OL  | N=747<br><br>1 year            | Primary:<br>Headache response rates at 1 and 2 hours<br><br>Secondary:<br>Safety and efficacy   | Primary:<br>Headache response rates at 1 and 2 hours were 43% and 73%, respectively ( <i>P</i> value not reported).<br><br>Secondary:<br>The most common adverse effects were back pain, bronchitis, and flu-like symptoms ( <i>P</i> value not reported).  |
| Diener et al <sup>16</sup><br><br>Almotriptan 12.5 mg<br><br>vs<br><br>placebo<br><br>All patients were poor responders to sumatriptan 50 mg. | DB, MC, PC, RCT<br><br>Eligible patients were adults aged 18 to 65 years who had suffered from migraine with or without aura for at least 1 year, and had experienced unsatisfactory responses to sumatriptan on at least two occasions | N=328<br><br>1 attack          | Primary:<br>Relief from headache at 2 hours after dosing<br><br>Secondary:<br>Pain-free efficacy at 2 hours, and use of rescue medication within 24 hours   | Primary:<br>In the almotriptan group, 47.5% of patients achieved pain relief at 2 hours after dosing which was significantly higher percentage than in the placebo group, 23.2% ( <i>P</i> <0.01).<br><br>Secondary:<br>A significantly higher number of patients treated with almotriptan 12.5 mg achieved pain-free status at 2 hours than with placebo (33.3% vs 14.1%; <i>P</i> <0.005).<br><br>Rescue medications were required by significantly fewer patients in the almotriptan group than with placebo (26.6% vs 46.9%; <i>P</i> <0.005).  |
| Pascual et al <sup>17</sup><br><br>Almotriptan 6.25 mg<br><br>vs<br><br>almotriptan 12.5 mg   | DB, OL<br><br>Patients 18-65 years old with at least 1 year history of migraine, with or without aura, all patients experienced 1-6 migraine attacks per month with at least 24 hours of freedom between                                | N=762<br><br>1 year            | Primary:<br>The primary measure of tolerability was the incidence of treatment-emergent adverse events (including abnormalities in clinical laboratory tests, ECG, vital signs or physical examination)<br><br>Secondary:<br>Percent of attacks | Primary:<br>During the study, 391 patients receiving active drug (51.3%) experienced at least 1 adverse event. Patients reported at least 1 adverse event in 11.0% of attacks treated. The incidence of adverse events decreased during the study; 30.7% of patients had at least 1 adverse event during the first 3 months in the study compared with only 21.5% during the last 3 months.<br><br>The majority (88.6%) of adverse events were of mild-to-moderate intensity. Only 28.8% of adverse events were considered to be possibly, probably or definitely related to the study drug. Of these drug-related events, those which occurred in at least 1.0% of patients were vomiting (2.1%), somnolence (1.7%), dizziness (1.6%), fatigue |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration  | End Points  | Results  |
|---|--|---------------------------------|---|--|
|   | attacks  |                                 | resolved (to mild or no pain) by 2 hours after dose (attacks of moderate/severe baseline intensity only)  | (1.4%) and nausea (1.4%; <i>P</i> values not reported).<br><br>Secondary:<br>Pain relief at 2 hours after the initial dose was achieved in 84.2% of moderate/severe attacks. Patients were pain free at 2 hours after dose in 58.2% of all attacks ( <i>P</i> values not reported).  |
| <p>Dowson et al<sup>18</sup></p> <p>Almotriptan 12.5 mg x 1 dose</p> <p>vs</p> <p>almotriptan 25 mg x 1 dose</p> <p>vs</p> <p>sumatriptan 100 mg x 1 dose</p> <p>vs</p> <p>placebo x 1 dose</p> <p>All study medications were administered during a migraine attack. A second dose was allowed if headache relapsed in 2-24 hours after first dose. Escape medication was allowed if pain persisted beyond 2 hours.</p> | <p>DB, MC, PC, PG, RCT, SD</p> <p>Patients 18-65 years old with migraine with or without aura for &gt;1 year</p> | <p>N=668</p> <p>Single dose</p> | <p>Primary:<br/>Relief from migraine pain at 2 hours after dosing</p> <p>Secondary:<br/>Relief from migraine pain at 1 hour, pain-free status at 1 and 2 hours, migraine recurrence within 24 hours post-dose, need for escape medication</p> | <p>Primary:<br/>Pain relief was higher in the treatment groups vs placebo as follows: almotriptan 12.5 mg=56.8% (achieved pain relief), almotriptan 25 mg=56.5%, sumatriptan 100 mg=63.7%, placebo=42.2% (<i>P</i> values not reported).</p> <p>Both doses of almotriptan were equivalent to sumatriptan 100 mg with the 90% CI interval inside the range of the equivalence region.</p> <p>Secondary:<br/>Relief from migraine pain at 1 hour was not statistically different for all three treatment arms.</p> <p>Migraine recurrence within 24 hours post-dose for patients with moderate pain at baseline was reported as follows: almotriptan 12.5 mg=22.7%, almotriptan 25 mg=14.9%, sumatriptan 100 mg=22.4%, placebo=16.7% (<i>P</i> values not reported).</p> <p>Migraine recurrence within 24 hours post-dose for patients with severe pain at baseline was reported as follows: almotriptan 12.5 mg=8.8%, almotriptan 25 mg=16.2%, sumatriptan 100 mg=28.9%, placebo=27.3% (<i>P</i> values not reported).</p> <p>The use of escape medication was reported as follows: almotriptan 12.5 mg=38.6%, almotriptan 25 mg=38.2%, sumatriptan 100 mg=32.4%, placebo=55.5% (<i>P</i> values not reported).</p> |

| Study and Drug Regimen   | Study Design and Demographics   | Sample Size and Study Duration  | End Points   | Results  |
|--|---|---------------------------------|--|--|
| <p>Dahlof et al<sup>19</sup></p> <p>Almotriptan 2 mg single dose given at onset of moderate or severe migraine attack</p> <p>vs</p> <p>almotriptan 6.25 mg single dose given at onset of moderate or severe migraine attack</p> <p>vs</p> <p>almotriptan 12.5 mg single dose given at onset of moderate or severe migraine attack</p> <p>vs</p> <p>almotriptan 25 mg single dose given at onset of moderate or severe migraine attack</p> <p>vs</p> <p>placebo single dose given at onset of moderate or severe migraine attack</p> <p>Another dose of study drug was allowed if pain severity</p> | <p>DB, MC, PC, PG, RCT</p> <p>Patients 18-65 years old with migraine with or without aura for &gt;1 year, migraines occurring one-six times per month</p> | <p>N=742</p> <p>Single dose</p> | <p>Primary:<br/>Change in headache pain intensity at 2 hours without rescue medication</p> <p>Secondary:<br/>Freedom from pain, relief from migraine-associated symptoms</p> | <p>Primary:<br/>Almotriptan demonstrated a dose-dependent increase in the number of patients with improvement in headache pain intensity (58.5% and 66.5% improvement for the 12.5 and 25 mg doses, respectively, compared to 32.5% for placebo; <math>P&lt;0.001</math>). Almotriptan 2 mg was equivalent to placebo.</p> <p>Secondary:<br/>With regards to freedom from pain, almotriptan produced a significant dose-dependent increase over placebo at 1, 1.5 and 2 hours (<math>P&lt;0.0001</math>).</p> <p>Almotriptan 12.5 mg produced significant improvement compared to placebo at 0.5 hours (<math>P&lt;0.0485</math>).</p> <p>Almotriptan demonstrated a significant dose-dependent improvement in pain-free state at 2 hours both with almotriptan 12.5 mg and almotriptan 25 mg compared to placebo (<math>P&lt;0.001</math>). A significantly better response was observed for patients with baseline moderate headache than patients with severe headache.</p> <p>A dose-dependent decrease in the incidence of migraine-associated symptoms was noted for almotriptan.</p> <p>The incidence of migraine recurrence was not significantly different among the treatment groups, ranging from 25.2% to 28.7%.</p> |

| Study and Drug Regimen   | Study Design and Demographics  | Sample Size and Study Duration | End Points  | Results   |
|--|--|--------------------------------|---|---|
| increased within 2-24 hours. Escape medication was allowed if pain did not decrease after 2 hours.   |  |                                |   |   |
| Dahlof et al <sup>20</sup><br><br>Almotriptan 2.0 mg<br><br>vs<br><br>almotriptan 5.0 mg<br><br>vs<br><br>almotriptan 6.25 mg<br><br>vs<br><br>almotriptan 12.5 mg<br><br>vs<br><br>almotriptan 25 mg<br><br>vs<br><br>almotriptan 100 mg<br><br>vs<br><br>almotriptan 150 mg<br><br>vs<br><br>placebo | Meta-analysis of 4 DB, PC, R, dose comparison studies<br><br>Male and female patients between 18 and 65 years of age who had at least a 6-month history of migraine, and experienced 1 to 6 migraine attacks per month | N=2,294<br><br>First attack    | Primary:<br>Efficacy, speed of onset and tolerability of almotriptan in the acute treatment of migraine; percentage (proportion) of patients achieving sustained pain free with no adverse events (no drug vs drug comparisons were made)<br><br>Secondary:<br>Not reported | Primary:<br>As early as 30 minutes after dosing, almotriptan 12.5 mg was significantly more effective than placebo for pain relief (14.9% vs 8.2%; $P<0.05$ ) and pain free (2.5% vs 0.7%; $P<0.05$ ).<br><br>At 2 hours, pain-relief rates were 56.0%, 63.7% and 66.0% for almotriptan 6.25, 12.5 and 25 mg, respectively, compared with 35.0% for placebo; 2-hour pain-free rates were 26.7%, 36.4% and 43.4% compared with 13.9% for placebo.<br><br>All almotriptan dosages were significantly more effective than placebo in eliminating migraine-associated symptoms ( $P<0.05$ ) and in achieving sustained pain relief up to 24 hours ( $P<0.05$ ).<br><br>The incidence of adverse events for almotriptan 6.25 and 12.5 mg was not significantly different from that of placebo.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration | End Points   | Results   |
|---|---|--------------------------------|--|---|
| Colman et al <sup>21</sup><br><br>Almotriptan 12.5 mg<br><br>vs<br><br>sumatriptan 50 mg    | DB, RCT<br><br>Patients aged 18-71 years who had not been treated previously with a triptan, suffering with migraine with or without aura for ≥6 months | N= 1,173<br><br>48 hours       | Primary:<br>Change in treatment satisfaction measure, functional status measure, and MqoLQ values from baseline to 48 hours<br><br>Secondary:<br>Not reported  | Primary:<br>There were no significant differences between the 2 treatment groups in terms of satisfaction with pain relief (mean score 50.85 for almotriptan and 52.10 for sumatriptan; $P=0.67$ ).<br><br>Functional status was not significantly different. Both groups improved by ~44 points on the 100-point functional status scale after 24 hours. Patients from both groups reported improvement in functional status after treatment, from marginally functional at onset of migraine (mean scores for almotriptan and sumatriptan, 42.54 and 42.50 respectively) to ~90% of normal (mean scores 86.49 and 86.99, respectively) at 24 hours.<br><br>Similarly, no difference was found between the 2 treatment groups in a comparison of MqoLQ at 24 hours after treatment.<br><br>Patients in the almotriptan group were significantly more satisfied and experienced fewer side effects than patients receiving sumatriptan ( $P=0.016$ ).<br><br>Secondary:<br>Not reported |
| Spierings et al <sup>22</sup><br><br>Almotriptan 12.5 mg<br><br>vs<br><br>sumatriptan 50 mg | DB, MC, PG, R<br><br>Men and women between 18 and 65 years who suffered from migraine with or without aura  | N=1,255<br><br>24 hours        | Primary:<br>Headache relief from moderate or severe to mild or no headache and pain-free status at 2 hours<br><br>Secondary:<br>Migraine relief and freedom from headache pain at 0.5 and 1 hours after intake of study medication, improvement of | Primary:<br>Headache relief at 2 hours was observed in 58.0% of patients in the almotriptan group and 57.3% of patients in the sumatriptan group with no significant difference between the groups. Pain-free response rate at 2 hours was observed in 17.9% of patients in the almotriptan group and 24.6% of patients in the sumatriptan group ( $P=0.005$ ) in favor of sumatriptan.<br><br>Secondary:<br>There was no significant difference between the groups with regards to relief from migraine-associated symptoms of nausea, vomiting, photophobia, and phonophobia.<br><br>Rescue medications were taken by 36.7% of almotriptan patients and   |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration | End Points   | Results   |
|---|--|--------------------------------|--|---|
|   |  |                                | migraine associated symptoms, incidence of migraine recurrence at 24 hours after dosing, and the use of rescue medication  | <p>33.2% of sumatriptan patients (<i>P</i> value not reported).</p> <p>Of the 343 responders in the almotriptan group, 27.4% experienced a migraine recurrence within 24 hours, compared to 24.0% of the 333 responders in the sumatriptan group. The differences were not statistically significant (<i>P</i> value not reported).</p>   |
| <p>Olesen et al<sup>23</sup></p> <p>Eletriptan 80 mg</p> <p>vs</p> <p>placebo</p> | <p>DB, PC, R</p> <p>Male and female patients aged 18 years and older with migraine with aura every 4 weeks</p> | <p>N=123</p> <p>24 hours</p>   | <p>Primary:</p> <p>Proportion of subjects not developing a migraine headache of moderate or severe intensity within 6 hours of dosing with a double-blind study drug</p> <p>Secondary:</p> <p>Time to headache development, duration of aura symptoms, use of second dose, response to the second dose, use of rescue medication, treatment acceptability, and time to rescue medication</p> | <p>Primary:</p> <p>Treatment with eletriptan during the aura phase was not effective in preventing the onset of moderate-to-severe headache post-aura. There was no significant difference in the proportions of patients developing a headache on eletriptan (61%) compared with placebo (46%; <i>P</i> value not reported).</p> <p>Secondary:</p> <p>Eletriptan did not increase the duration of the aura phase compared with placebo (0.7 hour vs 0.8 hour), nor was it associated with a significant delay in the median time to headache onset (1.3 hour vs 1.0 hour; <i>P</i> value not reported).</p> <p>A second dose of eletriptan 40 mg was permitted for patients in both the eletriptan and placebo treatment groups who developed a moderate-to-severe headache. Response rates to the 40-mg dose of eletriptan were similar in both (initial) treatment groups (<i>P</i> value not reported).</p> <p>Additional rescue medication was taken by 28% of patients initially randomized to eletriptan 80 mg, and by 17% of patients initially randomized to placebo (<i>P</i> value not reported).</p> <p>The percentage of patients rating study medication as acceptable was comparable for both eletriptan and placebo (76% vs 72%; <i>P</i> value not reported).</p> <p>There was no significant difference between groups on any efficacy measure.</p> |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration  | End Points   | Results  |
|---|---|---------------------------------|--|--|
| Farkkila et al <sup>24</sup><br><br>Eletriptan 40 mg<br><br>vs<br><br>eletriptan 80 mg<br><br>vs<br><br>placebo       | DB, MC, PC, R<br><br>Male and female subjects age ≥18 years with HIS diagnostic criteria for migraine, with or without aura                                     | N=446<br><br>3 migraine attacks | Primary:<br>2-hour headache response rates<br><br>Secondary:<br>Onset of action, 2-hour pain-free response rates, incidence of nausea, vomiting and headache recurrence, consistency of response   | Primary:<br>2-hour headache response, based on first-dose, first-attack data, was 59% for eletriptan 40 mg, 70% for eletriptan 80 mg and 30% for placebo ( $P<0.0001$ for both doses of eletriptan vs placebo; $P<0.05$ for eletriptan 80 mg vs eletriptan 40 mg).<br><br>Secondary:<br>Onset of action was rapid, with 1-hour headache response rates significantly higher for eletriptan 40 mg and eletriptan 80 mg vs placebo (40%, 48%, 15%; $P<0.0005$ ).<br><br>Both eletriptan 40 mg and eletriptan 80 mg were significantly better than placebo, based on first-dose, first-attack data, for 2-hour pain-free response (35%, 42% and 7%; $P<0.0001$ ).<br><br>Both eletriptan 40 mg and eletriptan 80 mg demonstrated significant consistency of response, with headache relief rates at 2 hours on at least two of three attacks of 66% and 72%, respectively, vs 15% on placebo ( $P<0.001$ ). |
| Garcia-Ramos et al <sup>25</sup><br><br>Eletriptan 40 mg<br><br>vs<br><br>naratriptan 2.5 mg<br><br>vs<br><br>placebo | DB, PG, R<br><br>Male or female adults, aged 18–80 years with migraine with or without aura and who reported a minimum of 1 acute migraine attack every 6 weeks | N=548<br><br>Single attack      | Primary:<br>Headache response at 2 hours after the first dose of study medication<br><br>Secondary:<br>Headache response at 0.5, 1, 4 and 24 hours; pain-free response at 0.5, 1, 2, 4 and 24 hours; presence or absence of associated symptoms at the same time-points; functional status; headache recurrence and time-to- | Primary:<br>Headache response rates at 2 hours and 4 hours, respectively, were 56% and 80% for eletriptan, 42% and 67% for naratriptan ( $P<0.01$ for both time-points vs eletriptan), and 31% and 44% for placebo ( $P<0.0001$ vs both active drugs at both time-points).<br><br>Secondary:<br>Headache response was also significantly higher for eletriptan at 1 hour and 4 hours, respectively, compared with both naratriptan (34% vs 25%; $P<0.05$ ; 80% vs 67%; $P<0.01$ ) and placebo (21%; $P<0.01$ ; 44%; $P<0.0001$ ).<br><br>Headache response rates were not significantly different from placebo at 30 minutes for either eletriptan (12% vs 5%; $P=0.063$ ) or for naratriptan (9%; $P=0.391$ vs placebo).<br><br>Eletriptan showed higher pain-free rates at both 2 and 4 hours (35%   |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points  | Results  |
|------------------------|-------------------------------|--------------------------------|---|--|
|                        |                               |                                | headache-recurrence; use of rescue medication and time-to-use; sustained headache; sustained pain-free response; global evaluation of medication; acceptability of study medication | <p>and 56%, respectively) compared with both naratriptan (18%; <math>P&lt;0.001</math> and 41%; <math>P&lt;0.01</math>) and placebo (19%; <math>P&lt;0.001</math>; 24%; <math>P&lt;0.0001</math>).</p> <p>By 1 hour, pain-free rates were significantly higher for eletriptan (12%) compared with naratriptan (6%; <math>P&lt;0.05</math>).</p> <p>Pain-free response for naratriptan was significantly higher than placebo at 4 hours (<math>P&lt;0.01</math>) but not at 2 hours.</p> <p>Eletriptan also showed a significantly greater pain-free response at 2 hours (35% vs 18%; <math>P&lt;0.001</math>) as well as lower use of rescue medication (15% vs 27%; <math>P&lt;0.01</math>) and higher sustained headache response at 24 hours (38%) compared with naratriptan (27%; <math>P&lt;0.05</math>) and placebo (19%; <math>P&lt;0.01</math>).</p> <p>Among patients who achieved a 2-hour headache response, headache recurrence rates were consistently low for eletriptan (29%), naratriptan (26%), and placebo (28%), with no significant differences among the 3 treatment groups. The proportion of patients taking a second dose of study medication for headache recurrence was lower for eletriptan and naratriptan (19% and 18%, respectively) than for placebo (26%). The proportion of patients reporting sustained headache response at 24 hours was significantly higher for eletriptan (38%) compared with both naratriptan (27%; <math>P&lt;0.05</math>) and placebo (19%; <math>P&lt;0.01</math>). The difference in sustained response was not significant for naratriptan vs placebo.</p> <p>The proportion of patients reporting a sustained pain-free response at 24 hours was significantly higher for eletriptan (22%) compared with both naratriptan (11%; <math>P&lt;0.05</math>) and placebo (12%; <math>P&lt;0.05</math>).</p> <p>Patients treated with eletriptan showed significantly better functional improvement at 2 hours compared with both naratriptan (60% vs 52%; <math>P=0.014</math>) and placebo (44%; <math>P&lt;0.001</math>). The difference in functional status was not significantly different for naratriptan vs</p> |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration           | End Points  | Results   |
|---|---|--|---|---|
|   |   |  |   | <p>placebo.</p> <p>Patient ratings of treatment acceptability (recorded at 24 hours for current vs prior migraine treatments) were significantly higher for eletriptan compared to both naratriptan (68% vs 50%; <math>P&lt;0.001</math>) and placebo (31%; <math>P&lt;0.0001</math>). Naratriptan also showed significantly higher acceptability compared to placebo (<math>P&lt;0.05</math>).</p> <p>The proportion of patients reporting treatment to be 'good-to-excellent' was significantly higher for eletriptan (70%) compared to both naratriptan (53%; <math>P&lt;0.001</math>) and placebo (33%; <math>P&lt;0.0001</math>). Naratriptan also showed significantly higher global ratings compared to placebo (<math>P&lt;0.001</math>).</p>   |
| <p>Sheftell et al<sup>26</sup></p> <p>Eletriptan 20 mg</p> <p>vs</p> <p>eletriptan 40 mg</p> <p>vs</p> <p>eletriptan 80 mg</p> <p>vs</p> <p>placebo</p> | <p>DB, MC, PC, PG, R</p> <p>Men and women over 18 years of age with a history of at least one typical attack of migraine with or without aura every 6 weeks</p> | <p>N=1,334</p> <p>3 migraine attacks</p> | <p>Primary:<br/>2-hour headache response for the first attack</p> <p>Secondary:<br/>Incidence of associated symptom relief, and pain-free, sustained pain-free, and consistency of response</p> | <p>Primary:<br/>Eletriptan 20, 40 and 80 mg achieved significantly (<math>P&lt;0.001</math>) better headache response rates than placebo at 2 hours (47%, 62% and 59%, respectively, versus 22%) and 4 hours (64%, 76% and 79%, respectively, versus 25%).</p> <p>Secondary:<br/>Two-hour pain-free response rates for eletriptan 20, 40 and 80 mg were 14%, 27% and 27%, respectively, compared with 4% for placebo (<math>P&lt;0.001</math>).</p> <p>Sustained pain-free response rates were significantly better for eletriptan 20 mg (10%), 40 mg (20%) and 80 mg (18%) compared with placebo (3%; <math>P&lt;0.001</math>).</p> <p>Eletriptan had a higher consistency of inpatient response than placebo in two of three (68% to 82%) and three of three attacks (32% to 60%) versus 16% and 8%, respectively (<math>P</math> value not reported).</p> <p>All eletriptan doses yielded significant functional improvement at 2 hours (<math>P&lt;0.001</math>).</p> |

| Study and Drug Regimen   | Study Design and Demographics  | Sample Size and Study Duration        | End Points  | Results   |
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| Diener et al <sup>27</sup><br><br>Eletriptan 40 mg<br><br>vs<br><br>eletriptan 80 mg<br><br>vs<br><br>ergotamine tartrate 2 mg, caffeine 200 mg (Cafergot®)<br><br>vs<br><br>placebo | DB, MC, PC, PG, R<br><br>Male or female patients aged 18–65 years, who experienced migraine with or without aura for at least 1 year; frequency of migraine attacks had to be at least 1 every 6 weeks but not more than 6 per month | N=733<br><br>24 hours                 | Primary:<br>Headache response (improvement from severe or moderate to mild or no pain) at 2 hours<br><br>Secondary:<br>Headache response at 1 hour, pain-free rates at 1 and 2 hours, functional hour impairment, functional response, and presence of migraine-associated symptoms or absence of nausea, vomiting, photophobia and phonophobia | Primary:<br>Significantly more eletriptan-treated patients (80 mg, 68%; 40 mg, 54%) than Cafergot®-treated patients (33%; $P<0.001$ ) reported headache response (improvement from moderate-to-severe to mild or no pain) at 2 hours.<br><br>Substantially more eletriptan recipients reported no pain (80 mg, 38%; 40 mg, 28%; Cafergot®, 10%; placebo, 5%; $P<0.001$ ).<br><br>Secondary:<br>Eletriptan headache response rates at 1 hour were significantly higher (80 mg, 39%; 40 mg, 29%; Cafergot®, 13%; placebo, 13%; $P<0.002$ for each comparison).<br><br>Both doses of eletriptan were significantly more effective than Cafergot® in reducing nausea ( $P<0.0001$ ), photophobia (80 mg; $P<0.0001$ ; 40 mg; $P<0.002$ ), phonophobia (80 mg; $P<0.0001$ ; 40 mg; $P<0.003$ ) and functional impairment ( $P\leq 0.001$ ) at 2 hours. |
| Steiner et al <sup>28</sup><br><br>Eletriptan 40 mg<br><br>vs<br><br>eletriptan 80 mg<br><br>vs<br><br>zolmitriptan 2.5 mg<br><br>vs<br><br>placebo                                  | DB, PC, PG, R<br><br>Male or female patients aged 18–65 years with migraine with or without aura   | N=1,312<br><br>Single migraine attack | Primary:<br>Headache response within 2 hours of taking the first dose of study medication<br><br>Secondary :<br>Headache-response rates at 0.5, 1 and 1.5 hours, pain-free rates at 0.5, 1, 1.5 and 2 hours, absence of associated symptoms at 0.5, 1, 1.5 and 2 hours, functional recovery at 1 and 2 hours, headache-                         | Primary:<br>On the primary efficacy end-point of headache response at 2 hours, eletriptan 80 mg (265/360, 74%) was significantly better than zolmitriptan 2.5 mg (224/376, 60%; $P<0.0001$ ) and placebo (30/135, 22%; $P<0.0001$ ).<br><br>Eletriptan 40 mg was more efficacious than placebo ( $P<0.0001$ ) at 2 hours (229/359, 64%) and 1 hour (101/361, 28%) but not significantly better than zolmitriptan 2.5 mg at any time point.<br><br>Eletriptan 80 mg was significantly better ( $P<0.01$ ) than eletriptan 40 mg in headache response at 2 hours.<br><br>Secondary:<br>On the secondary efficacy endpoint of 1 hour response rates, eletriptan 80 mg (149/369, 40%) was more efficacious than zolmitriptan 2.5 mg (93/371, 25%; $P<0.0001$ ) and placebo (7/134,  |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points  | Results  |
|------------------------|-------------------------------|--------------------------------|---|--|
|                        |                               |                                | recurrence rate, use of rescue medication, sustained headache response, sustained pain-free, patient's global evaluation of study medication at 24 hours on a 7-point Likert scale, acceptability of study medication | <p>5%; <math>P&lt;0.0001</math>).</p> <p>Pain-free rates for eletriptan 80 mg were better at both 2 hours (157/360, 44%) and 1 hour (44/369, 12%) compared to zolmitriptan (99/376, 26%; <math>P&lt;0.0001</math>; 21/371, 6%; <math>P&lt;0.01</math>) and placebo (8/135, 6%; <math>P&lt;0.0001</math>; 1/134, &lt;1.0%; <math>P&lt;0.01</math>). Eletriptan 40 mg was significantly better than placebo at 2 hours (115/359, 32%; <math>P&lt;0.0001</math>) and 1 hour (21/361, 6%; <math>P&lt;0.05</math>) but not zolmitriptan 2.5 mg.</p> <p>Eletriptan 80 mg was significantly better (<math>P&lt;0.01</math>) than eletriptan 40 mg in headache response and pain-free rates at 2 hours.</p> <p>Eletriptan 80 mg was significantly better (<math>P&lt;0.01</math>) than eletriptan 40 mg in pain-free rates at 2 hours.</p> <p>In the subsets with severe or moderate functional impairment at baseline (3 or 2 on the scale 0-3), all active treatments were better than placebo (<math>P&lt;0.0001</math>) at bringing improvement. Patients on eletriptan 80 mg (response rates: 194/285, 68% at 2 hours; 100/296, 34% at 1 hour) did better than those on zolmitriptan 2.5 mg (171/303, 56% at 2 hours; <math>P&lt;0.05</math>; 73/303, 24% at 1 hour; <math>P&lt;0.05</math>). Eletriptan 40 mg (181/296, 61%; 73/300, 24%) was not significantly different from zolmitriptan on this measure.</p> <p>In the subsets of patients achieving headache response by 2 hours, headache-recurrence rates were numerically lower for patients on eletriptan 80 mg (84/253, 33%; <math>P=0.271</math>) and significantly lower for patients on eletriptan 40 mg (65/225, 29%; <math>P&lt;0.05</math>) than for those on zolmitriptan (83/218, 38%). Both doses of eletriptan had significantly lower recurrence rates than placebo (16/31, 52%; <math>P&lt;0.05</math>).</p> <p>Significantly fewer patients used rescue medication after eletriptan 80 mg (53/390, 14%) than after zolmitriptan (101/395, 26%; <math>P&lt;0.0001</math>) or placebo (81/140, 58%; <math>P&lt;0.0001</math>). This was true of those taking eletriptan 40 mg also (76/387, 20%; <math>P&lt;0.05</math> vs zolmitriptan; <math>P&lt;0.0001</math></p> |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration                  | End Points   | Results  |
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|   |   |   |  | <p>vs placebo).</p> <p>More patients achieved headache response by 2 hours and continued to 24 hours without recurrence or use of rescue medication (sustained headache response) on eletriptan 80 mg (160/338, 47%; <math>P&lt;0.001</math>) and 40 mg (151/345, 44%; <math>P&lt;0.01</math>) than on zolmitriptan (125/362, 35%). Eletriptan 80 mg (<math>P&lt;0.0001</math>) and 40 mg (<math>P&lt;0.0001</math>), as well as zolmitriptan (<math>P&lt;0.0001</math>), were all significantly better than placebo (14/131, 11%).</p> <p>Sustained-pain-free rate was higher for eletriptan 80 mg (100/343, 29%) than for zolmitriptan (61/367, 17%; <math>P&lt;0.001</math>). Eletriptan 80 mg (<math>P&lt;0.0001</math>) and 40 mg (75/349, 22%; <math>P&lt;0.0001</math>), as well as zolmitriptan (<math>P&lt;0.01</math>), were better than placebo (6/134, 5%).</p> <p>Patients' ratings of treatment acceptability ('would use again') showed preferences for eletriptan 80 mg (232/381, 61%; <math>P&lt;0.05</math>) and 40 mg (244/379, 64%; <math>P&lt;0.01</math>) over zolmitriptan 2.5 mg (205/389, 53%).</p> <p>All active treatments were rated significantly better than placebo (26/137, 19%; <math>P&lt;0.0001</math>).</p> <p>On the 7-point global rating of study medication, analysis was of the percentage of patients in each group recording either "excellent" or "good". Eletriptan 80 mg (254/387, 66%) and 40 mg (243/380, 64%) were both rated more highly than zolmitriptan (214/389, 55%; <math>P&lt;0.01</math>). All active treatments scored significantly better than placebo (24/139, 17%; <math>P&lt;0.0001</math>).</p> |
| Goadsby et al <sup>29</sup><br><br>Eletriptan 20 mg<br><br>vs<br><br>eletriptan 40 mg | DB, PG, R<br><br>Male and female subjects, 18 years of age and older, who met the IHS criteria for migraine | N=692<br><br>Single migraine attack<br>24 hours | Primary:<br>Percentage of responders, operationally defined as any patient who, within 2 hours after ingesting study drug, | <p>Primary:<br/>Headache response rates 2 hours after dosing were 24% (30/126) for placebo, 55% (63/115) for sumatriptan 100 mg, 54% (70/129) for eletriptan 20 mg, 65% (76/117) for eletriptan 40 mg and 77% (91/118) for eletriptan 80 mg.</p> <p>There was a difference compared with placebo (<math>P&lt;0.001</math>) for all</p>   |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration         | End Points   | Results   |
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| vs<br>eletriptan 80 mg<br>vs<br>sumatriptan 100 mg<br>vs<br>placebo   | with or without aura   |  | reported improvement in headache intensity to mild or pain-free levels from a pretreatment level of moderate or severe<br><br>Secondary:<br>Not reported                               | doses of eletriptan.<br><br>There was a difference between sumatriptan 100 mg and eletriptan 80 mg ( $P<0.001$ ) at 2 hours.<br><br>Headache-free rates at 2 hours were better than placebo (6%; $P<0.001$ ) for both the 80-mg dose of eletriptan (37%) and the 40-mg dose (29%), with the 80-mg dose of eletriptan also being more efficacious than the 100-mg dose of sumatriptan (23%; $P<0.05$ ).<br><br>Secondary:<br>Not reported  |
| Mandema et al <sup>30</sup><br>Eletriptan 20 mg<br>vs<br>eletriptan 40 mg<br>vs<br>eletriptan 80 mg<br>vs<br>sumatriptan 25 mg<br>vs<br>sumatriptan 50 mg<br>vs<br>sumatriptan 100 mg | MA, PC<br><br>For inclusion in the analysis, each trial had to meet the following criteria: (1) DB, PC, and RCT; (2) treatment of moderate or severe migraine in adults within 8 hours of onset; (3) measurement of relief from migraine pain on a four point categorical scale of none, mild, moderate, severe; (4) includes efficacy results for the first attack; (5) no re-medication or rescue before 2 hours | N=11,400<br><br>Duration not specified | Primary:<br>Proportion of patients that achieved migraine pain relief up to 4 hours after treatment and proportion of patients that became pain free<br><br>Secondary:<br>Not reported | Primary:<br>The results of this analysis show a significant difference for eletriptan 40 mg compared to sumatriptan 100 mg at any point in time up to 4 hours after treatment ( $P$ value not reported).<br><br>The benefit of eletriptan 40 mg is greatest around 1.5–2 hours after treatment with an absolute difference at 2 hours of 9.1% (7.4%–11.5%) more patients achieving pain relief and 7.3% (5.8%–8.6%) more patient achieving pain free when compared to sumatriptan 100 mg ( $P$ value not reported).<br><br>An absolute benefit of more than 5% of patients is maintained from 45 minutes up to 4 hours after treatment for pain relief and from 1.5 hours up to 4 hours for pain-free response ( $P$ value not reported).<br><br>Eletriptan 20 mg was more efficacious than sumatriptan 50 mg and similar to sumatriptan 100 mg for pain relief, while it was similar to sumatriptan 50 mg for pain-free response ( $P$ value not reported).<br><br>The benefit of eletriptan 20 mg when compared to sumatriptan 50 mg is greatest around 1.5–2 hours after treatment with an absolute difference at 2 hours of 5.0% (2.9%–8.1%) more patients achieving pain relief ( $P$ value not reported). |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration | End Points  | Results  |
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| vs<br>sumatriptan 200 mg<br>vs<br>sumatriptan 300 mg<br>vs<br>placebo                       |  |                                |   | <p>An absolute benefit of more than 3% of patients was maintained from 1 hour up to 3 hours after treatment. No significant difference was found between eletriptan 20 mg and sumatriptan 50 mg for the fraction of patients that became pain free (<i>P</i> value not reported).</p> <p>No significant effect of encapsulation of sumatriptan was found on the time course of response up to 4 hours after treatment when compared to commercial sumatriptan (<i>P</i> value not reported).</p> <p>Secondary:<br/>Not reported</p>  |
| Mathew et al <sup>31</sup><br>Eletriptan 40 mg<br>vs<br>sumatriptan 100 mg<br>vs<br>placebo | DB, PC, PG, R<br>Men and women, aged 18 to 65 years, who met the IHS criteria for migraine with or without aura  | N=2,113<br>24 hours            | <p>Primary:<br/>The primary endpoint was 2-hour headache response</p> <p>Secondary:<br/>Headache response rates at 1 hour, pain-free rates, absence of associated symptoms, functional response at 1 and 2 hours, and sustained headache response</p> | <p>Primary:<br/>Headache response rates at 2 hours post-dose were significantly higher for eletriptan 40 mg (67%) than for sumatriptan 100 mg (59%; <i>P</i>&lt;0.001) and placebo (26%; <i>P</i>&lt;0.0001).</p> <p>Secondary:<br/>Eletriptan 40 mg consistently showed significantly better (<i>P</i>&lt;0.01) efficacy over sumatriptan 100 mg across secondary clinical outcomes, including 1-hour headache response; 2-hour pain-free response; absence of nausea, photophobia, and phonophobia; functional improvement; use of rescue medication; treatment acceptability; and sustained headache response (<i>P</i>&lt;0.05).</p> |
| Schoenen et al <sup>32</sup><br>Eletriptan 80 mg<br>vs<br>sumatriptan 6 mg SC               | OL, R, XO<br>Male and female patients 18–65 years of age that met the IHS criteria for migraine with or without aura, and suffered at least one acute attack every 6 weeks | N=311<br>3 migraine attacks    | <p>Primary:<br/>Patient preference for eletriptan versus sumatriptan SC</p> <p>Secondary:<br/>Change from pretreatment baseline in headache intensity; change from pretreatment baseline</p>  | <p>Primary:<br/>Fifty-one percent of patients preferred or greatly preferred eletriptan, while 43% preferred sumatriptan SC. When permitted to choose between eletriptan and sumatriptan SC for subsequent treatment, 78% of patients who had preferred eletriptan took eletriptan during the extension phase for all three of their attacks, while only 37% of patients who preferred sumatriptan SC took sumatriptan SC for all of their extension-phase attacks (<i>P</i>&lt;0.05).</p> <p>Secondary:<br/>Secondary efficacy measures showed comparable efficacy for each</p>   |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration | End Points  | Results   |
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|   |   |                                | in a 5-point patient-rated Global Impression of efficacy scale; the presence or absence of nausea, vomiting, photophobia and phonophobia; change in functional impairment scale; headache recurrence (and time to headache recurrence), between 2 and 24 hours after ingestion of study medication; time to use of rescue medication; sustained relief; acceptability of study medication | study medication, except for faster headache response and pain-free rates in favor of sumatriptan SC, and a significantly lower recurrence rate on eletriptan (25% vs 40%; $P<0.05$ ).  |
| Sandrini et al <sup>33</sup><br>Eletriptan 40 mg<br>vs<br>eletriptan 80 mg<br>vs<br>sumatriptan 50 mg<br>vs<br>sumatriptan 100 mg | DB, DD, MC, PC, PG, RCT<br><br>Men and women >18 years of age who were expected to have at least one attack of migraine with or without aura, every 6 weeks | N=1,008<br><br>3 attack study  | Primary:<br>Early headache response (at 1 hour) was the primary endpoint, 2-hour headache response<br><br>Secondary:<br>Headache response rates, functional improvement, patient acceptability  | Primary:<br>Headache response rates were 12% at 1 hour and 31% at 2 hours for placebo; 24% at 1 hour and 50% at 2 hours for sumatriptan 50 mg; 27% at 1 hour and 53% at 2 hours for sumatriptan 100 mg; 30% at 1 hour and 64% at 2 hours for eletriptan 40 mg; and 37% at 1 hour and 67% at 2 hours for eletriptan 80 mg.<br><br>More patients receiving eletriptan 80 mg achieved a 1-hour headache response than did patients receiving sumatriptan 50 mg ( $P<0.05$ ).<br><br>All doses of eletriptan were more efficacious than sumatriptan at 2 hours for headache response and complete pain relief ( $P<0.05$ ).<br><br>Secondary:<br>Significantly more patients on eletriptan 80 mg achieved headache response in all attacks than did patients receiving either sumatriptan dose. Eletriptan 40 mg was more efficacious than both sumatriptan |

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|   |  |  |   | doses in functional improvement ( $P<0.005$ ).<br><br>The higher efficacy of both eletriptan doses was associated with higher rates of patient acceptability than sumatriptan 50 mg ( $P<0.05$ ).  |
| Ryan et al <sup>34</sup><br><br>Frovatriptan 2.5 mg<br><br>vs<br><br>placebo  | DB, MA, PC, PG<br><br>Patients with migraine   | N=2,676<br><br>24 hours (up to 3 migraine attacks) | Primary:<br>Headache response at 2 hours<br><br>Secondary:<br>Time to headache recurrence, incidence of patients with 24-hour headache recurrence | Primary:<br>In all three studies, headache response 2 hours after frovatriptan dosing was significantly greater than that seen with placebo ( $P\leq 0.001$ ) with approximately a two-fold measure of effect over placebo for headache response at 2 and 4 hours post-dosing.<br><br>Secondary:<br>Time to headache response occurred within 1.5 hours in a substantial proportion of patients. The incidence of 24-hour headache recurrence with frovatriptan was low (10% to 25%).  |
| Cady et al <sup>35</sup><br><br>Frovatriptan 2.5 mg early use<br>dose 1: frovatriptan<br>dose 2: placebo<br><br>vs<br><br>frovatriptan 2.5 mg late use<br>dose 1: placebo<br>dose 2: frovatriptan | DB, MC, PC, XO<br><br>Patients had migraine history >1 year with 2 to 8 migraines in the previous 2 months | N=165<br><br>2 migraine attacks                    | Primary:<br>The incidence of no migraine headache 2 hours post dose<br><br>Secondary:<br>Comparison of early vs later use of frovatriptan         | Primary:<br>Twenty-eight percent and 20% of early frovatriptan users and placebo users, respectively, were headache free at 2 hours ( $P=0.04$ ).<br><br>Secondary:<br>Fifty percent of early users were pain free at 3 hours.<br><br>Early use of frovatriptan prevented mild migraine headaches from progressing to moderate or severe headaches ( $P$ value not reported).<br><br>Migraine recurrence was low, 4%-6%, regardless of treatment group ( $P$ value not reported).<br><br>During the 24 hours following the first dose, 64% of patients experienced nothing worse than mild functional impairment when frovatriptan was used early compared with 48% of patients when placebo was used early ( $P<0.001$ ). |
| Stark et al <sup>36</sup><br><br>Naratriptan 2.5 mg<br><br>vs   | Single blind for attack 1, DB, PC, PG, R for attack 2<br><br>Self-described poor                           | N=347<br><br>2 migraine attacks                    | Primary:<br>Conversion from moderate or severe pain to mild or no pain at 4 hours after the use   | Primary:<br>For attack 2, naratriptan was statistically more efficacious than placebo for the relief of headache pain (defined as mild or no pain) at 4 hours ( $P<0.001$ ).   |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration      | End Points  | Results  |
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| sumatriptan 50 mg<br>vs<br>placebo  | sumatriptan responders, had history of migraine >1 year  |                                     | of the double-blind test medication for the treatment of attack 2<br><br>Secondary:<br>Headache relief at 2 hours and complete pain relief at 4 hours, which include relief of other components of migraine syndrome  | Secondary:<br>Naratriptan was more efficacious than placebo at 2 hours for relief of headache ( $P=0.005$ ), but statistical significance was not shown for pain-free response ( $P>0.05$ ).   |
| Klassen et al <sup>37</sup><br><br>Naratriptan 0.1 mg<br>vs<br>naratriptan 0.25 mg<br>vs<br>naratriptan 1 mg<br>vs<br>naratriptan 2.5 mg<br>vs<br>placebo | DB, PC, PG, R<br><br>Men and women 18 to 65 years of age with at least a 1-year history of migraine with or without aura | N=613<br><br>Single migraine attack | Primary:<br>Percentage of patients who experienced headache relief (moderate or severe pain at dosing reduced to mild or no pain) 4 hours after the first dose of study medication<br><br>Secondary:<br>Examined at each measured time point through 4 hours post-dose, included the proportions of patients with headache relief, proportions of patients with meaningful relief, proportions with headache relief 8, 12, and 24 hours post-dose, the proportion | Primary:<br>Headache relief 4 hours post-dose was reported in 60% of patients receiving naratriptan 2.5 mg compared with 50%, 35%, 32% and 34% of patients receiving naratriptan 1 mg, 0.25 mg, 0.1 mg and placebo, respectively ( $P<0.05$ naratriptan 2.5 mg and 1 mg vs placebo, 1 mg vs 0.1 mg, and 2.5 mg vs 0.1 mg and 0.25 mg).<br><br>Secondary:<br>Clinical disability 4 hours post-dose was reported as mild or none for 70% of patients receiving naratriptan 2.5 mg compared with 63%, 47%, 48% and 48% of patients receiving naratriptan 1 mg, 0.25 mg, 0.1 mg or placebo, respectively ( $P<0.05$ naratriptan 2.5 mg and 1 mg vs placebo, 1 mg vs 0.1 mg and 2.5 mg vs 0.1 mg and 0.25 mg).<br>Four-hour efficacy for absence of nausea, photophobia, and phonophobia was similar to efficacy for headache relief at each dose.<br><br>The adverse event profile of each dose of naratriptan was similar to that of placebo. No clinically relevant change in any safety measure was reported. |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration | End Points   | Results   |
|---|--|--------------------------------|--|---|
|   |  |                                | taking rescue medication within 24 hours of initial dosing, and the proportion experiencing headache recurrence within 24 hours of initial dosing  |   |
| Gobel et al <sup>38</sup><br><br>Naratriptan 2.5 mg<br><br>vs<br><br>sumatriptan 100 mg | DB, R<br><br>Men and women 18-65 years old with >1 year history of migraine with or without aura, randomly assigned to treat 1 moderate or severe migraine attack in a nonclinical setting with one naratriptan 2.5 tablet and 1 attack with 1 sumatriptan 100 mg tablet | N=253<br><br>24 hours          | Primary:<br>Percent of patients with headache recurrence, percent of patients with 24-hour maintenance of headache relief<br><br>Secondary:<br>Percentage of patients experiencing headache relief, the percent of patients using rescue medication during the 24 hours after dosing, and the percentage of patients that took a second dose of study drug | Primary:<br>Headache recurrence for naratriptan was 45% and recurrence with sumatriptan was 57% (no significant statistical difference).<br><br>After 2 attacks, headache recurrence for naratriptan was 41% and for sumatriptan was 57%. The odds ratio for not experiencing recurrence after treatment with naratriptan relative to sumatriptan was 1.97 ( $P=0.005$ ; 95% CI, 1.24 to 3.15).<br><br>Twenty-four hour maintenance of headache relief was reported by 39% of patients given naratriptan and 34% of patients treated with sumatriptan (OR, 1.26; 95% CI, 0.86 to 1.85; $P=NS$ ).<br><br>Secondary:<br>Percentage of patients experiencing headache relief was 76% for patients treated with naratriptan 2.5 mg, and 84% in patients who received sumatriptan 100 mg (not significantly different).<br><br>The percent of patients who received rescue medications for inadequate relief up to 24 hours after dosing did not differ significantly between naratriptan-treated patients (21%) and sumatriptan-treated patients (16%) (OR, 1.47; 95% CI, 0.94 to 2.30).<br><br>The percent of patients that took a second dose of study drug did differ significantly. Forty percent of patients treated with naratriptan used a second dose of study medication after initial treatment, compared with 57% for sumatriptan ( $P<0.001$ ; OR, 0.51; 95% CI, 0.37 to 0.71). |

| Study and Drug Regimen   | Study Design and Demographics  | Sample Size and Study Duration      | End Points   | Results  |
|--|--|-------------------------------------|--|--|
| Ashcroft et al <sup>39</sup><br><br>Naratriptan 2.5 mg<br><br>vs<br><br>naratriptan 1 mg<br><br>vs<br><br>rizatriptan 10 mg<br><br>vs<br><br>sumatriptan 100 mg<br><br>vs<br><br>placebo | MA<br><br>Patients suffering from moderate or severe migraine attacks  | N=449<br><br>Single migraine attack | Primary:<br>Response rate ratios for headache relief, pain-free response and sustained relief (4-24 hours)<br><br>Secondary:<br>Adverse events were estimated with the RR, risk difference and number needed to harm   | Primary:<br>Pooled RR's relative to placebo for pain-free response at 2 and 4 hours for naratriptan 2.5 mg were 2.52 (95% CI, 1.78 to 3.57) and 2.58 (1.99 to 3.35), respectively.<br><br>Naratriptan 2.5 mg was more effective than naratriptan 1 mg; the corresponding RR's for pain-free response at 2 and 4 hours were 1.54 (95% CI, 1.28 to 1.86) and 1.35 (1.20 to 1.51), respectively.<br><br>Naratriptan 2.5 mg was less effective in pain-free response than either rizatriptan 10 mg at 4 hours (RR, 0.68; 95% CI, 0.55 to 0.85) or sumatriptan 100 mg at 4 hours (RR, 0.79; 95% CI, 0.67 to 0.93).<br><br>Secondary:<br>Significantly fewer patients experienced adverse effects with naratriptan 2.5 mg than with rizatriptan 10 mg (RR, 0.73; 95% CI, 0.56 to 0.97) or sumatriptan 100 mg (RR, 0.68; 95% CI, 0.55 to 0.86). |
| Mathew et al <sup>40</sup><br><br>Rizatriptan 10 mg<br><br>vs<br><br>placebo   | PC, R<br><br>Patients aged 20 to 64 years with migraine and a history of headache progressing to moderate or severe pain when no intervention was used | N=112<br><br>3 migraine attacks     | Primary:<br>Percentage of migraine attacks in which treatment produced a pain-free response at 2 hours after study drug administration<br><br>Secondary:<br>Pain-free response at 1 hour after administration, percentage of migraine attacks in which treatment provided a sustained pain-free response lasting | Primary:<br>Pain-free response at 2 hours after early treatment occurred in 151 of 216 attacks (70%) in the rizatriptan group and 24 of 109 attacks (22%) in the placebo group ( $P<0.01$ ).<br><br>Secondary:<br>Pain-free response at 1 hour occurred in 97 attacks (45%) in the rizatriptan group, compared with 9 (8%) in the placebo group ( $P<0.01$ ).<br><br>When the attacks were categorized by headache severity at the time of treatment, the pain-free response at 2 hours was higher for mild attacks than for moderate or severe attacks ( $P<0.01$ ).<br><br>Sustained pain-free response after treatment was significantly higher for attacks treated with rizatriptan (60%) than for those treated with placebo (17%; $P<0.001$ ).   |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration        | End Points   | Results  |
|---|---|---------------------------------------|--|--|
|   |   |                                       | between 2 and 24 hours after administration  |  |
| Ferrari et al <sup>41</sup><br><br>Rizatriptan 5 mg<br>vs<br>rizatriptan 10 mg<br>vs<br>placebo | MA of DB, R<br><br>Outpatients who had at least a 6-month history of migraine                               | N=4,816<br><br>Single migraine attack | Primary:<br>Pain relief, associated migraine symptoms and functional disability (all measured immediately before dosing and at 0.5, 1, 1.5 and 2 hours), headache recurrence<br><br>Secondary:<br>Not reported | Primary:<br>At 2 hours, rizatriptan 10 mg was significantly more effective than placebo for pain relief (71% vs 38%; $P<0.001$ ), and for elimination of pain, nausea, photophobia, phonophobia and functional disability.<br><br>The benefit was maintained over 24 hours; 37% of patients on rizatriptan 10 mg had sustained pain relief vs 18% for placebo ( $P<0.001$ ).<br><br>Rizatriptan 10 mg was also more effective than rizatriptan 5 mg, with a significant difference at 2 hours on all measures except for elimination of nausea.<br><br>The benefit was maintained over 24 hours; 38% of patients on rizatriptan 10 mg had sustained pain relief vs 32% for rizatriptan 5 mg ( $P=0.001$ ).<br><br>Secondary:<br>Not reported |
| Oldman et al <sup>42</sup><br><br>Rizatriptan 5 mg<br>vs<br>rizatriptan 10 mg<br>vs<br>placebo  | MA<br><br>Men and women in good health aged >18 years with moderate or severe migraine with or without aura | N=2,626<br><br>Single dose            | Primary:<br>Headache response at 2 hours, headache response at 1 hour, pain-free response at 2 hours, sustained relief over 24 hours<br><br>Secondary:<br>Not reported   | Primary:<br>Headache response (moderate to severe pain reduced to mild or none) at 2 hours were reported as follows:<br>Rizatriptan 5 mg: RB, 1.8 (1.6 to 2.0); NNT, 3.9 (3.3 to 4.7); n=1,646.<br>Rizatriptan 10 mg: RB, 2.2 (2.0 to 2.4); NNT, 2.7 (2.4 to 2.9); n=2,770.<br><br>Headache response at one hour was reported as follows:<br>Rizatriptan 5 mg: RB, 1.6 (1.4 to 1.9); NNT, 7.2 (5.4 to 10); n=1,646.<br>Rizatriptan 10 mg: RB, 1.9 (1.6 to 2.1); NNT, 4.9 (4.2 to 6.0); n=2,770.<br><br>Pain-free response (moderate to severe pain reduced to none) at two hours was noted as follows:   |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration      | End Points   | Results  |
|---|---|-------------------------------------|--|--|
|   |   |                                     |  | <p>Rizatriptan 5 mg: RB, 3.4 (2.6 to 4.4); NNT, 4.7 (4.0 to 5.7); n=1,646.<br/> Rizatriptan 10 mg: RB, 4.8 (3.8 to 5.9); NNT, 3.1 (2.9 to 3.4); n=2,770.</p> <p>Sustained relief over 24 hours (headache response at 2 hours, sustained for 24 hours with no rescue medication and no second dose of study medication) was noted as follows:<br/> Rizatriptan 5 mg: RB, 1.5 (1.3 to 1.8); NNT, 8.3 (6.0 to 14); n=1,450.<br/> Rizatriptan 10 mg: RB, 1.7 (1.5 to 2.0); NNT, 5.6 (4.5 to 7.4); n=1,677.</p> <p>Secondary:<br/> Not reported</p>   |
| Kolodny et al <sup>43</sup><br><br>Rizatriptan 5 mg<br><br>vs<br><br>rizatriptan 10 mg<br><br>vs<br><br>sumatriptan 25 mg<br><br>vs<br><br>sumatriptan 50 mg<br><br>vs<br><br>placebo | DB, PC, R, two-attack study<br><br>Men and women in good health aged >18 years with at least 6-month history of migraine with or without aura | N=1,447<br><br>5 days               | Primary:<br>Time to pain relief during the 2 hours after taking study drug<br><br>Secondary:<br>2-hour pain relief status and the presence of associated symptoms at 2 hours | Primary:<br>The primary efficacy variable, expressed as the hazard ratio of rizatriptan 10 mg vs sumatriptan 50 mg, was 1.10 (95% CI, 0.96 to 1.26; $P=0.161$ ).<br><br>Rizatriptan 5 mg was statistically ( $P=0.007$ ) more efficacious than sumatriptan 25 mg; the hazard ratio of rizatriptan 5 mg vs sumatriptan 25 mg was 1.22 (95% CI, 1.06 to 1.41).<br><br>Secondary:<br>Rizatriptan 10 mg-treated patients had significantly less nausea ( $P=0.004$ ) compared with those treated with sumatriptan 50 mg.<br><br>For all other secondary measures at 2-hours, rizatriptan 10 mg was not statistically different than sumatriptan 50 mg. |
| Lainez et al <sup>44</sup><br><br>Rizatriptan 10 mg   | MC, OL, XO<br><br>Patients aged 18–65 years with a  | N=372<br><br>Single migraine attack | Primary:<br>Patient preference was analyzed for all patients who treated both  | Primary:<br>Significantly more ( $P\leq 0.001$ ) patients preferred rizatriptan 10 mg wafer (61.1%; 95% CI, 55.7 to 66.3) to eletriptan 40-mg tablet (38.9%; 95% CI, 33.7 to 44.3). The most common reason given for   |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration | End Points  | Results   |
|---|---|--------------------------------|---|---|
| vs<br>eletriptan 40 mg  | history of at least 6 months of migraine, with or without aura  |                                | attacks and who expressed a preference for one medication over the other<br><br>Secondary:<br>Not reported  | preference of either treatment was speed of headache relief. At 2 hours, 80% and 69% of patients reported that rizatriptan and eletriptan, respectively, were convenient or very convenient to take (mean convenience score 1.99 vs 2.31, respectively; $P \leq 0.001$ ).<br><br>Secondary:<br>Not reported   |
| Adelman et al <sup>45</sup><br><br>Rizatriptan 10 mg<br><br>vs<br><br>naratriptan 2.5 mg<br><br>vs<br><br>zolmitriptan 2.5 mg<br><br>vs<br><br>sumatriptan 25 mg<br><br>vs<br><br>sumatriptan 50 mg<br><br>vs<br><br>sumatriptan 100 mg | DB, PC<br><br>5 trials<br><br>Outpatients who had at least a 6-month history of migraine with or without aura | N=4,064<br><br>24 hours        | Primary:<br>Pain-free response at 2 hours, symptom-free response at 2 hours, 24-hour sustained pain-free response<br><br>Secondary:<br>Adverse events | Primary:<br>Pain-free rates at 2 hours were significantly higher for rizatriptan than for all other triptans included in the studies. Percent of patients who were pain-free ranged from 38%-45% for rizatriptan 10 mg and 21%-36% for all other triptans. The statistical significance of these differences is noted below.<br>Rizatriptan 10 mg vs sumatriptan 100 mg ( $P=0.019$ ).<br>Rizatriptan 10 mg vs sumatriptan 50 mg ( $P=0.009$ ).<br>Rizatriptan 10 mg vs sumatriptan 25 mg ( $P<0.001$ ).<br>Rizatriptan 10 mg vs naratriptan 2.5 mg ( $P<0.001$ ).<br>Rizatriptan 10 mg vs zolmitriptan 2.5 mg ( $P=0.041$ ).<br><br>Two hours after the dose, significantly more patients taking rizatriptan 10 mg were symptom free than were patients taking other triptans. The percentage of patients with freedom from pain and associated symptoms ranged from 30% to 33% for rizatriptan 10 mg and from 11% to 28% for the other triptans. The statistical significance is noted below.<br><br>Rizatriptan 10 mg vs sumatriptan 100 mg ( $P=0.002$ ).<br>Rizatriptan 10 mg vs sumatriptan 50 mg ( $P=0.003$ ).<br>Rizatriptan 10 mg vs sumatriptan 25 mg ( $P<0.001$ ).<br>Rizatriptan 10 mg vs naratriptan 2.5 mg ( $P<0.001$ ).<br>Rizatriptan 10 mg vs zolmitriptan 2.5 mg ( $P=0.042$ ).<br><br>More patients taking rizatriptan had a 24-hour sustained pain-free response than did patients taking other triptans. The statistical significance is noted below.<br>Rizatriptan 10 mg vs sumatriptan 100 mg ( $P=0.112$ ). |

| Study and Drug Regimen   | Study Design and Demographics  | Sample Size and Study Duration             | End Points  | Results  |
|--|--|--|---|--|
|  |  |  |   | <p>Rizatriptan 10 mg vs sumatriptan 50 mg (<math>P=0.015</math>).<br/> Rizatriptan 10 mg vs sumatriptan 25 mg (<math>P=0.005</math>).<br/> Rizatriptan 10 mg vs naratriptan 2.5 mg (<math>P=0.004</math>).<br/> Rizatriptan 10 mg vs zolmitriptan 2.5 mg (<math>P=0.013</math>).</p> <p>Secondary:<br/> Incidence of drug-related adverse events were as follows:<br/> Rizatriptan 10 mg vs sumatriptan 100 mg; 33% vs 41% (<math>P=0.014</math>).<br/> Rizatriptan 10 mg vs sumatriptan 50 mg; 37% vs 35% (<math>P=0.671</math>).<br/> Rizatriptan 10 mg vs sumatriptan 25 mg; 37% vs 31% (<math>P=0.043</math>).<br/> Rizatriptan 10 mg vs naratriptan 2.5 mg; 27% vs 19% (<math>P=0.079</math>).<br/> Rizatriptan 10 mg vs zolmitriptan 2.5 mg; 25% vs 28% (<math>P=0.410</math>).</p>  |
| <p>Bomhof et al<sup>46</sup></p> <p>Rizatriptan 10 mg</p> <p>vs</p> <p>naratriptan 2.5 mg</p> <p>vs</p> <p>placebo</p> | <p>DD, MC, PC, R, double-masked</p> <p>Patients aged 18-65 years who met IHS criteria for migraine with or without aura, a 6-month history of migraine and usually experienced 1-8 attacks per month</p> | <p>N=552</p> <p>Single migraine attack</p> | <p>Primary:<br/> Time to headache relief within 2 hours</p> <p>Secondary:<br/> Headache relief and pain free up to 2 hours, associated symptoms, functional disability, satisfaction with medication at 2 hours, need for additional medication from 2 to 24 hours, 24-hour quality of life, safety</p> | <p>Primary:<br/> Rizatriptan 10 mg was more effective than naratriptan 2.5 mg on the primary efficacy measure of time to headache relief within 2 hours. HR, 1.62 (95% CI, 1.26 to 2.09; <math>P&lt;0.001</math>).</p> <p>Secondary:<br/> Headache relief at 2 hours was 68.7% with rizatriptan and 48.4% with naratriptan (<math>P&lt;0.001</math>).</p> <p>In patients with migraine associated symptoms at baseline, rizatriptan gave earlier relief than naratriptan from nausea, photophobia, and phonophobia within 2 hours, with HR of 1.53 (95% CI, 1.11 to 2.11; <math>P=0.009</math>), 1.57 (95% CI, 1.13 to 2.19; <math>P=0.007</math>), and 1.61 (95% CI, 1.15 to 2.27; <math>P=0.006</math>) respectively.</p> <p>Rizatriptan was better than naratriptan with regard to time to no functional disability, with HR of 1.96 (95% CI, 1.36 to 2.82; <math>P&lt;0.001</math>).</p> <p>Patients on rizatriptan were more satisfied with their medication than those on naratriptan at 2 hour means scores 3.55 vs 4.21; <math>P&lt;0.001</math>.</p> <p>Fewer patients in both active treatment groups needed additional medications than those taking placebo (<math>P&lt;0.001</math>), while there was no statistically significant difference between active agents (<math>P=0.068</math>).</p> |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration    | End Points   | Results   |
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|   |   |                                   |  | <p>The overall incidence of any clinical adverse event was significantly higher in the rizatriptan group than in the naratriptan and placebo groups (<math>P&lt;0.05</math>).</p> <p>Rizatriptan and naratriptan were significantly better than placebo on all five quality-of-life domains (<math>P&lt;0.01</math>).</p> <p>Both active treatments were effective compared to placebo. Both active treatments were well tolerated.</p>   |
| <p>Lipton et al<sup>47</sup></p> <p>Rizatriptan 10 mg</p> <p>vs</p> <p>sumatriptan 100 mg</p> <p>vs</p> <p>sumatriptan 50 mg</p> <p>vs</p> <p>sumatriptan 25 mg</p> <p>vs</p> <p>naratriptan 2.5 mg</p> <p>vs</p> <p>zolmitriptan 2.5 mg</p> <p>vs</p> <p>placebo</p> | <p>MA of 5 trials</p> <p>Men and women in good health aged &gt;18 years with history of migraine with or without aura</p> | <p>N=4,097</p> <p>Single dose</p> | <p>Primary:</p> <p>Relief of nausea in those who had it at baseline and emergence of nausea in those who were free of it at baseline</p> <p>Secondary:</p> <p>Not reported</p> | <p>Primary:</p> <p>Approximately 60% of patients in each treatment group had nausea at baseline. In those patients with nausea at baseline, significantly more patients treated with rizatriptan 10 mg were free of nausea at 2 hours compared with sumatriptan 100 mg (66% vs 58%; <math>P=0.043</math>), sumatriptan 50 mg (68% vs 57%; <math>P=0.010</math>), sumatriptan 25 mg (68% vs 59%; <math>P=0.017</math>), and naratriptan 2.5 mg (59% vs 45%; <math>P=0.014</math>).</p> <p>Averaging over the four post treatment time points in the first 2 hours, significantly more patients treated with rizatriptan 10 mg were free of nausea compared with sumatriptan 100 mg (<math>P=0.004</math>), sumatriptan 50 mg (<math>P=0.001</math>), and naratriptan 2.5 mg (<math>P=0.015</math>).</p> <p>No significant differences in nausea relief were seen between rizatriptan 10 mg and zolmitriptan 2.5 mg, either at 2 hours (65% vs 61%; <math>P=0.210</math>) or over the first 2 hours (<math>P=0.781</math>).</p> <p>Rates of treatment-emergent nausea at 2 hours ranged from 11% to 18% with placebo, from 5% to 13% with rizatriptan 10 mg and from 10% to 20% with other comparator triptans.</p> <p>Secondary:</p> <p>Not reported</p> |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration        | End Points  | Results  |
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| Cady et al <sup>48</sup><br><br>Sumatriptan 6 mg SC<br><br>vs<br><br>placebo  | PC, R<br><br>Adult patients with history of migraine with or without aura         | N=1,104<br><br>Duration not specified | Primary:<br>1-hour headache response rate<br><br>Secondary:<br>Complete relief of headache, clinical disability, and reduction in other migraine symptoms | Primary:<br>Sumatriptan 6 mg SC produced a response (defined as mild pain or no pain) rate of 70%, compared with 22% for placebo ( $P<0.001$ ) and was more effective than placebo in totally eliminating migraine headache at 60 minutes (49% vs 9%; $P<0.001$ ).<br><br>Secondary:<br>Clinical disability improved more with sumatriptan (76%) than with placebo (34%; $P<0.001$ ).<br><br>Sumatriptan 6 mg SC was effective in reducing other symptoms such as nausea, vomiting, and photophobia.   |
| SC Sumatriptan International Study Group <sup>49</sup><br><br>Sumatriptan 6 mg SC<br><br>vs<br><br>sumatriptan 8 mg SC<br><br>vs<br><br>placebo | DB, PC, PG, R<br><br>Adult patients with history of migraine with or without aura | N=639<br><br>Duration not specified   | Primary:<br>Severity of headache at 60 minutes and 120 minutes<br><br>Secondary:<br>Not reported  | Primary:<br>After 60 minutes, the severity of headache pain declined in 72% of the 422 patients given 6 mg of sumatriptan, 79% of the 109 patients given 8 mg of sumatriptan, and 25% of the 105 patients who received placebo (3 patients were not evaluable; $P$ value not reported).<br><br>Compared with patients receiving placebo, 47% more patients who received 6 mg of sumatriptan and 54% more patients who received 8 mg of sumatriptan had less severe headaches ( $P<0.001$ ).<br><br>After 120 minutes, 86% to 92% of the 511 patients receiving sumatriptan felt headache severity improve, compared with 37% of the 104 patients who were given placebo once or twice ( $P<0.001$ ).<br><br>Secondary:<br>Not reported |
| Oral Sumatriptan International Multi-Dose Study Group <sup>50</sup><br><br>Sumatriptan 100 mg PO<br><br>vs                                      | DB, PC, PG<br><br>Adult patients with history of migraine with or without aura    | N=233<br><br>Duration not specified   | Primary:<br>Headache relief at 2 and 4 hours<br><br>Secondary:<br>Pain free at 2 hours, improvement in headache severity at 1                             | Primary:<br>Sumatriptan was significantly more effective than placebo at 2 hours (50% vs 19%; $P<0.001$ ) and at 4 hours (75% vs 30%; $P<0.001$ ).<br><br>Secondary:<br>In the sumatriptan group, 59% of the patients opted to take a second dose compared with 80% of the placebo arm ( $P<0.001$ ). More patients treated with sumatriptan than with placebo were pain free by 2 hours   |

| Study and Drug Regimen   | Study Design and Demographics   | Sample Size and Study Duration                       | End Points  | Results  |
|--|---|--|---|--|
| <p>placebo</p> <p>One tablet at onset of headache, one tablet 2 hours later if headache persists, and one tablet if the headache came back within 24 hours.</p>    |   |  | hour post-dose, number of patients needing two or three doses   | <p>(26% vs 5%; <math>P&lt;0.001</math>) and by 4 hours (48% vs 13%; <math>P&lt;0.001</math>).</p> <p>Improvement in headache severity by 1 hour post-dose was seen in 42% of sumatriptan patients and 17% of placebo patients. There was no difference between groups in the number of patients who took a third tablet if the headache recurred within 24 hours (<math>P=0.535</math>).</p>   |
| <p>Cutler et al<sup>51</sup></p> <p>Sumatriptan 25 mg PO</p> <p>vs</p> <p>sumatriptan 50 mg PO</p> <p>vs</p> <p>sumatriptan 100 mg PO</p> <p>vs</p> <p>placebo</p> | <p>DB, PC, PG, RCT</p> <p>Adult patients with history of migraine with or without aura</p>    | <p>N=259</p> <p>Single attack study</p>              | <p>Primary:</p> <p>Headache relief by 2 hours</p> <p>Secondary:</p> <p>Headache relief by 4 hours</p> | <p>Primary:</p> <p>By 2 hours, 50% to 56% of the patients who had received sumatriptan (any dosage) and 26% of the patients receiving placebo experienced relief (<math>P&lt;0.05</math>).</p> <p>Secondary:</p> <p>By 4 hours, 68% to 71% of the patients treated with sumatriptan and 38% of the patients who received placebo experienced relief (<math>P&lt;0.05</math>).</p>  |
| <p>Salonen et al<sup>52</sup></p> <p>Sumatriptan 1 mg IN</p> <p>vs</p> <p>sumatriptan 5 mg IN</p> <p>vs</p> <p>sumatriptan 10 mg IN</p> <p>vs</p>                  | <p>Two DB, MC, PC, PG</p> <p>Adult patients with history of migraine with or without aura</p> | <p>N=245</p> <p>N=210</p> <p>Single attack study</p> | <p>Primary:</p> <p>Headache relief at 2 hours</p> <p>Secondary:</p> <p>Not reported</p>               | <p>Primary:</p> <p>In both studies, headache severity had significantly improved at 120 minutes after doses of 10-40 mg sumatriptan compared to placebo (<math>P&lt;0.05</math>) and the greatest efficacy rates were obtained with 20 mg sumatriptan.</p> <p>With 20 mg sumatriptan, 78% and 74% of patients experienced headache relief in one- and two-nostril studies, respectively, compared with 35% and 42%, respectively, of those in the placebo groups.</p> <p>The 10-, 20-, and 40-mg doses were significantly more effective than placebo (<math>P&lt;0.01</math>, <math>P&lt;0.001</math>, <math>P&lt;0.05</math>, respectively).</p> |

| Study and Drug Regimen   | Study Design and Demographics   | Sample Size and Study Duration     | End Points  | Results   |
|--|---|------------------------------------|---|---|
| sumatriptan 20 mg IN<br><br>vs<br><br>sumatriptan 40 mg IN<br><br>vs<br><br>placebo<br><br>Study medication taken as a single dose in first study and as a divided dose in the second study. |   |                                    |   | Secondary:<br>Not reported  |
| Winner et al <sup>53</sup><br><br>Sumatriptan 50 mg PO<br><br>vs<br><br>sumatriptan 100 mg PO<br><br>vs<br><br>placebo   | MA of 6 DB, PC, R trials<br><br>Patients between 18 and 65 years of age, had at least a 1-year history of migraine with or without aura | N=2,297<br><br>Single attack study | Primary:<br>Proportion of patients reporting a pain free result 2 hours post-dose<br><br>Secondary:<br>Migraine-free 2 hours post-dose, worsening pain 2 hours post-dose, sustained pain-free results from 2-24 hours post-dose | Primary:<br>A pain-free result 2 hours post-dose was reported by significantly more patients who took either dose of sumatriptan tablets compared with placebo and by significantly more patients who took the 100-mg dose compared with the 50-mg dose (50 mg, 49%; 100 mg, 58%; placebo, 24%; $P<0.001$ , both sumatriptan doses vs placebo, and 100 mg vs 50 mg).<br><br>Secondary:<br>The proportion of patients who were migraine-free at 2 hours post-dose was 42% for sumatriptan 50 mg, 47% for sumatriptan 100 mg, and 20% for placebo ( $P<0.05$ for both sumatriptan doses vs placebo).<br><br>The proportion of patients reporting worsening of pain 2 hours post-dose was 26% for sumatriptan 50 mg, 21% for sumatriptan 100 mg and 46% for placebo ( $P<0.05$ for both sumatriptan doses vs placebo).<br><br>Sustained pain-free results from 2 through 24 hours post-dose were 30% for sumatriptan 50 mg, 35% for sumatriptan 100 mg, and 12% for placebo ( $P<0.05$ for both sumatriptan doses vs placebo). |

| Study and Drug Regimen  | Study Design and Demographics                           | Sample Size and Study Duration   | End Points   | Results   |
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| Gershovich et al <sup>54</sup><br><br>Sumatriptan<br>to<br>rizatriptan ODT  | RETRO<br><br>Patients aged 18 years and older           | N=457 initiated conversion from sumatriptan to rizatriptan ODT; 315 were randomly sampled for a satisfaction questionnaire<br><br>180 day medication conversion period; 180 day follow-up period | Primary:<br>Successful conversion rate, medication preference<br><br>Secondary:<br>Not reported                    | Primary:<br>The total number of successful conversions from sumatriptan to rizatriptan ODT (214/457 [47%]) correlated to the number of successful conversions among the questionnaire group (173/315 [55%]) returned the questionnaire; 82/173 [47%] had successful conversion; $P=0.969$ .<br><br>Among the patients that were successfully converted to rizatriptan ODT and responded to the questionnaire, 68.0% preferred the rizatriptan ODT compared to the sumatriptan; whereas 8.5% of patients who failed conversion rated rizatriptan ODT as their preferred medication ( $P<0.001$ ).<br><br>Successfully-converted patients reported faster and more complete headache relief with rizatriptan ODT (51.9% and 45.0% of the time, respectively [ $P<0.001$ ]). Failed-conversion respondents reported that sumatriptan yielded faster and more complete headache relief 78.3% and 75.9% of the time, respectively ( $P<0.001$ ).<br><br>Secondary:<br>Not reported |
| Loder et al <sup>55</sup><br><br>Sumatriptan 50 mg tablet<br>vs<br>rizatriptan ODT 10 mg<br><br>Patients treated first migraine with ODT and second with sumatriptan. | MC, OL, RCT, XO<br><br>Patients aged 18 years and older | N=524<br><br>7 days  | Primary:<br>Patient preference<br><br>Secondary:<br>Head pain severity, functional disability, headache recurrence | Primary:<br>No preference for either therapy was reported in 10 of 386 patients (2.6%). Of the remaining 374 patients 57% preferred rizatriptan ODT 10 mg and 43% preferred sumatriptan 50 mg tablet ( $P=0.009$ ).<br><br>Secondary:<br>A significant greater percentage of patients reported pain relief after taking ODT than sumatriptan at 45 and 60 minutes post dose (38% vs 29% and 58% vs 49%, respectively; $P<0.01$ )<br><br>A significantly greater percentage of patients taking ODT reported a pain-free status at 60 and 120 minutes post dose (23% vs 17% [ $P<0.05$ ] and 60% vs 52% [ $P<0.01$ ]), respectively.<br><br>Significantly more patients reported normal function following  |

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|  |  |   |  | <p>treatment with ODT than with sumatriptan 60 minutes (36% vs 27%; <math>P=0.004</math>) and 120 minutes (70% vs 64%; <math>P=0.029</math>) post-dose.</p> <p>The overall rate of headache recurrence was similar in both treatment groups.</p>   |
| <p>McCrory et al<sup>56</sup></p> <p>Sumatriptan 100 mg<br/>vs<br/>sumatriptan 50 mg<br/>vs<br/>sumatriptan 25 mg<br/>vs<br/>placebo</p> | <p>MA, PC</p> <p>Adult patients with history of migraine with or without aura</p>                              | <p>N=16,200</p> <p>Single attacks</p>                 | <p>Primary:<br/>2-hour pain-free response, headache relief/headache intensity, and functional disability, headache recurrence, adverse events</p> <p>Secondary:<br/>Not reported</p> | <p>Primary:<br/>Sixteen trials were placebo comparisons and showed that sumatriptan in doses of 100 mg (14 trials), 50 mg (5 trials), and 25 mg (3 trials) provided significantly better pain-free response (100 mg and 25 mg only), headache relief, and relief of disability at 2 hours than placebo.</p> <p>NNT's for pain-free response at 2 hours were 5.1 (3.9 to 7.1) for the 100-mg dose (n=2,221) and 7.5 (2.7 to 142.0) for the 25-mg dose (n=131); there was no significant difference between the 50-mg dose and placebo for this outcome (n=127).</p> <p>For headache relief at 2 hours, NNT's were 3.4 (3.0 to 4.0), 3.2 (2.4 to 5.1), and 3.4 (2.3 to 6.6) for sumatriptan 100 mg (n=2,940), 50 mg (n=420), and 25 mg (n=226), respectively.</p> <p>Adverse events were more common with sumatriptan 100 mg than with placebo (RR, 0.14 [0.09 to 0.20]; NNH, 7.1 [5.0 to 11.1]; n=3172). RR's for the 50- and 25-mg vs placebo comparisons were not statistically significant.</p> <p>Secondary:<br/>Not reported</p> |
| <p>Cady et al<sup>57</sup></p> <p>Sumatriptan 25 mg PO<br/>vs<br/>sumatriptan 50 mg PO</p>   | <p>DB, MA, PC</p> <p>Patients with <math>\geq 1</math> headache which was treated early when pain was mild</p> | <p>N=92</p> <p>118 headaches</p> <p>Single attack</p> | <p>Primary:<br/>Pain-free response 2 and 4 hours after dosing</p> <p>Secondary:<br/>Use of a second dose of medication, clinical</p>   | <p>Primary:<br/>Pain-free response was higher 2 hours after dosing with sumatriptan 50 mg (51%) or 100 mg (67%; <math>P&lt;0.05</math>) compared with placebo (28%), and were higher with early treatment of mild pain compared with treatment of moderate/severe pain at 2 hours (sumatriptan 50 mg: mild pain, 51%; moderate/severe pain, 31%; <math>P&lt;0.05</math>; sumatriptan 100 mg: mild pain 67%; moderate/severe pain, 36%) and 4 hours (50 mg: 75% vs 56%; 100 mg: 90% vs 61%; <math>P&lt;0.05</math>).</p>  |

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| vs<br>sumatriptan 100 mg PO<br>vs<br>ergotamine 2 mg plus caffeine 200 mg<br>vs<br>aspirin 900 mg plus metoclopramide 10 mg<br>vs<br>placebo  |  |                                | disability migraine-associated symptoms, meaningful pain relief (patient-defined), time to meaningful relief, sustained pain-free response, and proportion of attacks in which pain had worsened 2 and 4 hours after dosing, all of which were compared in headaches treated during mild versus moderate/severe pain          | Secondary:<br>Early intervention also resulted in less re-dosing than when moderate/severe pain was treated (50 mg: 21% vs 32%; 100 mg: 20% vs 29%).<br><br>More attacks treated early with sumatriptan 50 or 100 mg were associated with normal function 4 hours after dosing compared with placebo (70% and 93% vs 46%, respectively).<br><br>Sustained pain-free response rates 2 to 24 hours after early dosing with sumatriptan 50 or 100 mg were also higher (34% and 53%, respectively) compared with treatment of moderate/severe pain (19% and 24%, respectively).<br><br>Early treatment with sumatriptan 100 mg produced significantly higher pain-free rates at 2 hours after dosing ( $P<0.001$ ) than did ergotamine plus caffeine (69% vs 34%, respectively) or aspirin plus metoclopramide 73% vs 25%, respectively). |
| Geraud et al <sup>58</sup><br>Zolmitriptan 5 mg<br>vs<br>sumatriptan 100 mg<br>vs<br>placebo<br><br>Use of escape medication was permitted 2 hours post-dose if symptoms persisted. | DB, MC, PC, R<br><br>Treatment naïve migraine patients 18-65 years old with established diagnosis of migraine with or without aura for >1 year | N=1,058<br><br>24 hours        | Primary:<br>Complete headache response rates in acute treatment (defined as a reduction in headache pain from moderate/severe at baseline to mild or no pain 2 hours after taking study drug with no moderate or severe recurrences at 24 hours<br><br>Secondary:<br>Compare headache responses at 1, 2 and 4 hours post-dose | Primary:<br>Complete headache response (2-24 hours) was 39% for zolmitriptan, 38% for sumatriptan and 32% for placebo (no statistical difference).<br><br>In patients with moderate headache, response was greater with zolmitriptan (48%) than placebo (27%; $P=0.01$ ).<br><br>In patients with moderate headache there was no significant difference in complete response with zolmitriptan (48%) vs sumatriptan (40%).<br><br>In patients with moderate headache, response was not statistically different with zolmitriptan (48%) vs sumatriptan (40%).<br><br>For patients with severe baseline headache, there was no significant difference in complete response rates between placebo (44%) and either active treatment (27% for zolmitriptan and 35% sumatriptan).  |

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|  |   |                                |   | Secondary:<br>Active treatment groups were significantly more effective than placebo for 1-, 2-, and 4-hour headache response; ( $P<0.05$ vs placebo).   |
| Diener et al <sup>59</sup><br><br>Zolmitriptan 2.5 mg ODT<br><br>One dose was used to treat migraine headache; if headache recurred, a second dose was allowed after an interval of at least 2 hours from initial dosing.                        | OS<br><br>Patients aged 9-95 years with migraines   | N=14,543<br><br>2 years        | Primary:<br>Efficacy evaluation<br><br>Secondary:<br>Not reported   | Primary:<br>Headache pain improved in 96% of patients after taking zolmitriptan ODT, and the mean time to headache improvement was $51\pm44$ minutes ( $P$ value not reported).<br><br>Physicians' assessment determined that 90% of patients had either good or very good efficacy with zolmitriptan ODT ( $P$ value not reported).<br><br>Secondary:<br>Not reported   |
| Spierings et al <sup>60</sup><br><br>Zolmitriptan 5 mg ODT<br><br>vs<br><br>placebo<br><br>One dose was used to treat migraine headache; if there was inadequate relief or if the headache returned, a second dose was allowed 2-24 hours later. | DB, MC, PC, PG, RCT<br><br>Patients aged 18-65 years with at least 2 migraine headaches per month of moderate to severe intensity in addition to less than 10 days of non-migraine headaches per month for the 3 months prior to enrollment | N=656<br><br>6 weeks           | Primary:<br>Migraine headache response at 30 minutes<br><br>Secondary:<br>Speed of onset of headache response, duration of response | Primary:<br>The percentages of zolmitriptan and placebo patients with reduced migraine headache intensity (decreased from "moderate" or "severe" to "mild" or "no pain," as assessed at 30 minutes) were 16.5% (102/620 headaches) and 12.5% (81/647), respectively ( $P=0.048$ ).<br><br>Secondary:<br>At the 1-hour interval, the difference in the percentages of zolmitriptan and placebo patients with reduced migraine headache intensity (from "moderate" or "severe" to "mild" or "no pain") was statistically significant, with 41.1% (253/615) in the zolmitriptan group and 22.9% (147/642) in the placebo group ( $P<0.0001$ ). This difference was also consistent at the 2-hour mark: 59.0% (347/588) for zolmitriptan and 30.6% (193/631; $P<0.0001$ ).<br><br>A greater number of patients achieved sustained headache response (defined as a response maintained for 24 hours) with zolmitriptan compared to placebo, with rates of 42.5% and 16.4%, ( $P<0.0001$ ).<br><br>The percentage of patients that returned to normal activities was greater for the zolmitriptan group compared to placebo, with rates of 51.8% and 25.7%, respectively, at the 2-hour mark ( $P<0.0001$ ). |

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| Loder et al <sup>61</sup><br><br>Zolmitriptan 2.5 mg ODT (studies A and B)<br><br>or<br><br>zolmitriptan 5 mg ODT (study C)<br><br>vs<br><br>placebo | 3 DB, MC, PC, RCT<br><br>Patients with moderate to severe headaches (study A and C)<br><br>Patients who had a migraine attack and who were instructed to treat it as soon as possible (study B) | N=470 (study A)<br><br>N=565 (study B)<br><br>N=670 (study C)<br><br>24 hours | Primary:<br>Headache response (study A); pain-free rate at 2 hours (study B); migraine headache response at 30 minutes (study C)<br><br>Secondary:<br>Headache response at 30 minutes (study A); reduction of headache intensity (studies A and B); pain-free rate at 2 hours (studies A and C); resumption of normal activities (studies B and C) | Primary:<br>In study A, headache response at 2 hours, or the reduction in headache intensity from “moderate” or “severe” to “mild” or “no pain,” was greater for the zolmitriptan 2.5 mg ODT group compared to placebo (63% vs 22%; $P<0.0001$ ).<br><br>For study B, pain-free status at the 2-hour interval was achieved in 40.1% of the zolmitriptan patients and 19.8% of the placebo group ( $P<0.001$ ). At the 24-hour mark, this was maintained in 31.1% of the zolmitriptan patients and 14.6% of placebo patients ( $P<0.001$ ).<br><br>In study C, the percentage of zolmitriptan 5 mg ODT and placebo patients with reduced migraine headache intensity from “moderate” or “severe” to “mild” or “no pain” at 30 minutes were 16% and 13%, respectively ( $P<0.05$ ).<br><br>Secondary:<br>In study A, the percentage of zolmitriptan 2.5 mg ODT and placebo patients with reduced migraine headache intensity from “moderate” or “severe” to “mild” or “no pain” at 30 minutes were 16% and 10%, respectively ( $P=0.054$ ).<br><br>Collective results data from studies A and B showed a greater reduction of headache intensity (excluding mild-intensity attacks) at 30 minutes for the zolmitriptan ODT group compared to placebo (20.1% vs. 12.7%; $P<0.005$ ).<br><br>In study A, pain-free status at the 2-hour interval was achieved in 27% of the zolmitriptan 2.5 mg ODT patients and 7% of the placebo group ( $P<0.0001$ ). In study C, pain-free status at the 2-hour interval was achieved in 31% of the zolmitriptan 5 mg ODT patients and 11% of the placebo group ( $P<0.0001$ ).<br><br>Patients were able to resume normal activities 2 hours post-treatment in study B in 55.8% of the zolmitriptan ODT-treated cases compared to 34.0% of placebo-treated patients ( $P<0.001$ ). In study C, there was |

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|  |   |   |   | a greater percentage of patients that were able to resume normal activities 2 hours post-treatment in the zolmitriptan group compared to placebo (51.8% vs 25.7%; $P<0.0001$ ).  |
| Dowson et al <sup>62</sup><br><br>Zolmitriptan 2.5 mg ODT<br><br>vs<br><br>sumatriptan 50 mg tablet<br><br>or<br><br>rizatriptan 10 mg ODT<br><br>or<br><br>placebo                    | RCT, PC (vs placebo); OL, RCT, XO<br><br>Patients with migraines  | N=470<br>(vs placebo)<br><br>N=168<br>(vs sumatriptan)<br><br>N=171<br>(vs rizatriptan ODT)<br><br>12 weeks<br>(vs sumatriptan) | Primary:<br>Patient preference<br><br>Secondary:<br>Not reported  | Primary:<br>In the trial of zolmitriptan ODT vs placebo, 70% of patients preferred the ODT formulation compared to conventional tablets ( $P$ value not reported).<br><br>In terms of patient preference, there was a greater percentage of patients that preferred the zolmitriptan ODT compared to sumatriptan (60.1% vs 39.9%; $P=0.013$ ). Patients also found zolmitriptan ODT to be more efficacious compared to sumatriptan (76.7% vs 63.4%; $P=0.006$ ).<br><br>Patient preference for zolmitriptan ODT was greater than that of rizatriptan ODT (70% vs 27%; $P<0.001$ ).<br><br>Secondary:<br>Not reported   |
| Charlesworth et al <sup>63</sup><br><br>Zolmitriptan 0.5 mg IN<br><br>vs<br><br>zolmitriptan 1.0 mg IN<br><br>vs<br><br>zolmitriptan 2.5 mg IN<br><br>vs<br><br>zolmitriptan 5.0 mg IN | DB, DD, MC, PC, PG, RCT<br><br>Patients aged 18-65 years with migraine with or without aura (defined by IHS), minimum 1-year history of migraine symptoms, with an age of onset of migraine <50 years and an average of 1-6 migraine attacks per month during the 2 | N=1,547<br><br>Duration not specified   | Primary:<br>2-hour headache response<br><br>Secondary:<br>Early headache response at 15, 30 and 45 minutes, headache response at 1 and 4 hours post-dose, pain-free rates at 15, 30 and 45 minutes and 1, 2 and 4 post-dose | Primary:<br>The 2-hour headache response was reported to be the following: placebo 31% and zolmitriptan IN 70% ( $P\leq 0.01$ ), 59% ( $P\leq 0.01$ ), 55% ( $P\leq 0.01$ ) and 42% ( $P\leq 0.0008$ ) for 5.0, 2.5, 1.0 and 0.5 mg, respectively.<br><br>Zolmitriptan IN 5.0 mg was more effective than zolmitriptan 2.5 mg oral tablet (61%; $P<0.05$ ). Comparisons of the other doses of zolmitriptan IN to the oral tablet were not statistically significant.<br><br>Secondary:<br>The nasal spray at doses of 5.0 and 2.5 mg showed a rapid onset of action, with a significant difference in headache response compared with placebo from 15 minutes through 4 hours after administration. At 15 minutes, early headache response was 5% for placebo, 11% for zolmitriptan 5.0 mg IN ( $P=0.0115$ ), and 8% for zolmitriptan 2.5 mg IN ( $P=0.0261$ ). |

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| vs<br>zolmitriptan 2.5 mg oral tablet<br><br>vs<br>placebo       | months preceding the study   |                                   |   | Zolmitriptan 5.0 mg IN produced a significantly faster headache response than the 2.5 mg oral tablet from 15 minutes through 2 hours. The other nasal spray doses were not statistically different than the 2.5 mg oral tablet.<br><br>Zolmitriptan IN resulted in pain-free rates that were dose dependent. While all doses $\geq 1.0$ mg produced significant pain-free outcomes from 30 minutes vs placebo, only the 5.0 mg dose produced pain-free rates significantly better than the 2.5 mg oral tablet.  |
| Dowson et al <sup>64</sup><br><br>Zolmitriptan 5.0 mg IN         | DB, PG, RCT, XO<br><br>Patients 18-65 years with migraine with or without aura, previous participation in a dose-ranging study, 1-year history of migraine symptoms, with an age of onset of migraine <50 years and an average of 1-6 migraine attacks per month during the 2 months preceding the study | N=1,093<br>(783 XO)<br><br>1 year | Primary:<br>Tolerability (incidence and nature of all serious and nonserious adverse events)<br><br>Secondary:<br>Efficacy measured at 90-day intervals (2-hour headache response, pain-free response rate) | Primary:<br>Adverse events occurred in 22.1% of attacks treated with zolmitriptan 5.0 mg IN, and the majority were of short duration and mild or moderate intensity. Unusual taste and nasopharyngeal events were reported in 11.0% and 5.5% of attacks, respectively.<br><br>Only 1.9% of patients withdrew from the 12-month trial due to adverse events. Serious adverse events occurred in 0.2% of attacks treated. There was no evidence of increased incidence of adverse events with increasing duration of treatment.<br><br>Secondary:<br>Efficacy was consistent over time with 2-hour headache response rates of 73%, 74%, 75% and 74% during the four 90-day periods.<br><br>Long-term usage of zolmitriptan 5 mg IN was associated with a consistently effective response, with 58% of patients experiencing a 2-hour headache response in over 75% of attacks.<br><br>Pain-free response rates were also consistent over each 90-day period (52% to 56%). |
| Ferrari et al <sup>65</sup><br><br>Almotriptan 12.5 mg<br><br>vs | MA of 53 RCT<br><br>Randomized, double blind, controlled clinical  | N=24,089<br><br>Duration varied   | Primary:<br>Headache response at 2 hours, pain-free results at 2 hours, sustained pain-free   | Primary:<br>Headache response results at 2 hours (mean % [95% CI]) for sumatriptan 100 mg are 59.0 (57.3 to 60.8).<br><br>5-HT <sub>1</sub> agonists with better efficacy than sumatriptan 100 mg are:  |

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| eletriptan 20 mg<br>vs<br>eletriptan 40 mg<br>vs<br>eletriptan 80 mg<br>vs<br>frovatriptan 2.5 mg<br>vs<br>naratriptan 2.5 mg<br>vs<br>rizatriptan 5 mg<br>vs<br>rizatriptan 10 mg<br>vs<br>sumatriptan 25 mg<br>vs<br>sumatriptan 50 mg<br>vs | trials which included the treatment of moderate or severe migraine attacks within 8 hours of onset in migraine patients aged 18-65 years, treated with an oral triptan at a recommended clinical dose |                                | response<br><br>Secondary:<br>Adverse events | Rizatriptan 10 mg, 68.6 (66.9 to 70.4).<br>Eletriptan 80 mg, 65.8 (63.6 to 68.3).<br><br>5-HT <sub>1</sub> agonists with similar efficacy to sumatriptan 100 mg:<br>Almotriptan 12.5 mg, 61.2 (57.6 to 64.8).<br>Eletriptan 40 mg, 60.2 (58.0 to 62.4).<br>Zolmitriptan 2.5 mg, 63.5 (60.8 to 66.2).<br>Zolmitriptan 5 mg, 62.8 (60.0 to 65.6).<br>Rizatriptan 5 mg, 62.4 (60.2 to 64.5).<br><br>5-HT <sub>1</sub> agonists with lower efficacy to sumatriptan 100 mg:<br>Sumatriptan 25 mg, 56.0 (53.1 to 58.9).<br>Naratriptan 2.5 mg, 48.6 (45.7 to 51.4).<br>Eletriptan 20 mg, 48.9 (44.5 to 53.3).<br>Frovatriptan 2.5 mg, 41.5 (39.3 to 43.8).<br><br>Pain-free results at 2 hours (mean % [95% CI]) for sumatriptan 100 mg are 28.9 (27.2 to 30.5).<br><br>5-HT <sub>1</sub> agonists with higher rates than sumatriptan 100 mg are:<br>Almotriptan 12.5 mg, 61.2 (NA).<br>Eletriptan 80 mg, 33.0 (30.5 to 35.4).<br>Rizatriptan 10 mg, 40.1 (38.3 to 42.0).<br><br>5-HT <sub>1</sub> agonists with lower rates than sumatriptan 100 mg are:<br>Sumatriptan 25 mg, 23.4 (21.0 to 25.9).<br>Naratriptan 2.5 mg, 22.4 (20.0 to 24.7).<br>Eletriptan 20 mg, 16.4 (13.2 to 19.7).<br><br>All other triptans did not differ from sumatriptan 100 mg.<br><br>Sustained pain-free results (mean % [95% CI]) for sumatriptan 100 mg are 20.0 (18.2 to 21.3).<br><br>5-HT <sub>1</sub> agonists with higher rates than sumatriptan 100 mg are:<br>Almotriptan 12.5 mg, 25.9 (22.7 to 29.1). |

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| zolmitriptan 2.5 mg<br><br>vs<br><br>zolmitriptan 5 mg<br><br>vs<br><br>sumatriptan 100 mg<br><br>vs<br><br>placebo |  |  |  | <p>Rizatriptan 10 mg, 25.3 (23.7 to 26.9).<br/>Eletriptan 80 mg, 25.0 (22.8 to 27.2).</p> <p>5-HT<sub>1</sub> agonists with lower rates than sumatriptan 100 mg are:<br/>Eletriptan 20 mg, 10.6 (7.7 to 13.5).<br/>Sumatriptan 25 mg, 16.7 (14.5 to 18.9).<br/>Naratriptan 2.5 mg, 15.9 (13.4 to 18.5).</p> <p>No differences were found with other triptan doses.</p> <p>Secondary:<br/>Adverse effects – placebo subtracted adverse effects (mean [95% CI]) for sumatriptan 100 mg: 13.2 (8.6 to 17.8).</p> <p>5-HT<sub>1</sub> agonists with lower rates than sumatriptan 100 mg are:<br/>Almotriptan 12.5 mg, 1.8 (-2.5 to 6.2).<br/>Naratriptan 2.5 mg, 2.4 (-2.2 to 7.0).</p> <p>Central nervous system adverse effects-placebo subtracted adverse effects (mean [95% CI]) for sumatriptan 100 mg: 6.3 (3.2 to 9.5).</p> <p>5-HT<sub>1</sub> agonist with higher central nervous system adverse effect rates than sumatriptan 100 mg was eletriptan 80 mg: 14.6 (10.2 to 19.0)</p> <p>Rates for all other triptans and doses largely overlap.</p> <p>5-HT<sub>1</sub> agonist with lower central nervous system adverse effect rates than sumatriptan 100 mg was almotriptan 12.5 mg: -1.5 (-3.9 to 1.0).</p> <p>Rates for all other triptans and doses largely overlap.</p> |
| Brandes et al <sup>66</sup><br><br>Combination sumatriptan 85 mg/ naproxen sodium 500 mg 1 tablet administered at   | DB, MC, PC, PG, RCT<br><br>Men and women 18 to 65 years old, | Trial 1:<br>N=1,677<br><br>Trial 2:<br>N=1,736 | Primary:<br>Efficacy of sumatriptan/naproxen compared to placebo (2 hour headache relief | Primary:<br>Headache relief 2 hours post-dose:<br>Trial 1: sumatriptan/naproxen significantly more effective; 65% vs placebo 28% ( $P<0.001$ ), sumatriptan 55% ( $P=0.009$ ) and naproxen 44% ( $P<0.001$ ).  |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration      | End Points   | Results  |
|---|---|-------------------------------------|--|--|
| <p>onset of moderate to severe migraine</p> <p>vs</p> <p>sumatriptan 85 mg 1 tablet administered at onset of moderate to severe migraine</p> <p>vs</p> <p>naproxen sodium 500 mg 1 tablet administered at onset of moderate to severe migraine</p> <p>vs</p> <p>placebo</p> | <p>with a 6 month history of migraine with or without aura, with an average of 2 to 6 moderate or severe episodes monthly 3 months prior to study onset</p> | <p>Single attack administration</p> | <p>and 2 hour post dose absence of photophobia, phonophobia and nausea, efficacy of sumatriptan/naproxen compared to sumatriptan and naproxen monotherapy (2 hour headache relief and sustained pain free response</p> <p>Secondary:<br/>2 hour pain free response, sustained headache relief, sustained absence of nausea, photophobia, phonophobia, use of rescue medications, headache recurrence 24 hour incidence of vomiting</p> | <p>Trial 2: sumatriptan/naproxen significantly more effective; vs 57%, placebo 29% (<math>P&lt;0.001</math>), sumatriptan 50% (<math>P=0.03</math>) and naproxen 43% (<math>P&lt;0.001</math>).</p> <p>2 hour post-dose absence of photophobia, phonophobia and nausea:<br/>Trial 1: sumatriptan/naproxen significantly more effective than placebo (58%, 61%, 71% vs 36%, 38%, 65%) (<math>P&lt;0.001</math> for all measures).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective than placebo (50%, 56%, 65% vs 32%, 34%, 64%) (<math>P&lt;0.001</math> for all measures).</p> <p>Sustained pain free response:<br/>Trial 1: sumatriptan/naproxen significantly more effective; 25% vs sumatriptan 16% (<math>P&lt;0.01</math>) and naproxen 10% (<math>P&lt;0.001</math>).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective; 23% vs sumatriptan 14% and naproxen 10% (<math>P&lt;0.001</math> for all measures).</p> <p>Secondary:<br/>2 hour pain free response:<br/>Trial 1: sumatriptan/naproxen significantly more effective; 34% vs sumatriptan 25% (<math>P=0.009</math>), naproxen 15% (<math>P</math> value not reported) and placebo 9% (<math>P&lt;0.001</math>).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective; 30% vs sumatriptan 23% (<math>P=0.009</math>), naproxen 16% (<math>P</math> value not reported) and placebo 10% (<math>P&lt;0.001</math>).</p> <p>Sustained headache relief:<br/>Trial 1: sumatriptan/naproxen significantly more effective; 48% vs sumatriptan 35% (<math>P&lt;0.001</math>), naproxen 30% (<math>P</math> value not reported), placebo 18% (<math>P&lt;0.001</math>).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results  |
|------------------------|-------------------------------|--------------------------------|------------|--|
|                        |                               |                                |            | <p>Trial 2: sumatriptan/naproxen 44%, sumatriptan 33% (<math>P=0.002</math>), naproxen 28% (<math>P</math> value not reported), placebo 17% (<math>P&lt;0.001</math>).</p> <p>Sustained absence of nausea, photophobia, phonophobia:<br/>           Trial 1: Patients randomized to sumatriptan/naproxen experienced sustained benefit compared to placebo (<math>P&lt;0.001</math> for all measures) and compared to sumatriptan (<math>P=0.002</math>, <math>P=0.002</math>, <math>P&lt;0.001</math>).</p> <p>Trial 2: sumatriptan/naproxen exhibited significant sustained benefit compared to placebo (<math>P&lt;0.001</math>). No significant difference in sustained absence of nausea compared to sumatriptan (<math>P=0.20</math>). Significant difference in sustained absence of photophobia (<math>P=0.05</math>) and phonophobia (<math>P=0.01</math>).</p> <p>Use of rescue medications:<br/>           Trial 1: percentage of patients who used rescue medications significantly less in the sumatriptan/naproxen group; 22% vs 32% sumatriptan (<math>P=0.004</math>), 38% naproxen (<math>P</math> value not reported) and 53% placebo (<math>P&lt;0.001</math>).</p> <p>Trial 2: percentage of patients who used rescue medications significantly less in the sumatriptan/naproxen group; 23% vs 38% sumatriptan (<math>P&lt;0.001</math>), 39% naproxen (<math>P</math> value not reported) and 58% placebo (<math>P&lt;0.001</math>).</p> <p>Recurrence of headache:<br/>           Trial 1: number of patients with headache recurrence; sumatriptan/naproxen 30, sumatriptan 47, naproxen 25, placebo 26.</p> <p>Trial 2: number of patients with headache recurrence; sumatriptan/naproxen 26, sumatriptan 34, naproxen 35, placebo 34.</p> <p>24 hour incidence of vomiting:<br/>           Trial 1: sumatriptan/naproxen not significantly more effective than sumatriptan; 4% vs 7% (<math>P=0.14</math>).</p> |

| Study and Drug Regimen  | Study Design and Demographics   | Sample Size and Study Duration  | End Points  | Results  |
|---|---|---|---|--|
|   |   |   |   | Trial 2: sumatriptan/naproxen significantly more effective than sumatriptan; 4% vs 9% ( $P=0.004$ ).   |
| <p>Landy et al<sup>67</sup></p> <p>Combination sumatriptan 85 mg/naproxen 500 mg 1 tablet administered at onset of moderate to severe migraine</p> <p>vs</p> <p>sumatriptan 85 mg 1 tablet administered at onset of moderate to severe migraine</p> <p>vs</p> <p>naproxen 500 mg 1 tablet administered at onset of moderate to severe migraine</p> <p>vs</p> <p>placebo</p> | <p>DB,MC, PC, PG, RCT</p> <p>Men and women 18 to 65 years old with a <math>\geq 6</math> month history of migraine attacks, who had first migraine attack before age of 50, and experienced average of 2 to 6 moderate to severe attacks in previous 3 months</p> | <p>Trial 1<br/>N=1,468</p> <p>Trial 2<br/>N=1,441</p> <p>Single attack administration</p> | <p>Primary:<br/>Ability to function, productivity assessed by 24 hour post dose PAQ, patient satisfaction assessed by 24 hour post dose PPMQ</p> <p>Secondary:<br/>Not reported</p> | <p>Primary:<br/>Ability to function:<br/>Trial 1: significant difference between sumatriptan/naproxen vs naproxen and placebo during hour 2 through 5 post-dose (<math>P&lt;0.001</math>).</p> <p>Trial 2: significant difference between sumatriptan/naproxen vs naproxen and placebo (<math>P&lt;0.001</math>) and sumatriptan (<math>P&lt;0.005</math>) 2-5 hours post-dose.</p> <p>24 hour post-dose PAQ productivity:<br/>Trial 1: significantly less total lost productivity with sumatriptan/naproxen, 33%, vs naproxen (<math>P=0.016</math>) and placebo (<math>P&lt;0.001</math>).</p> <p>Trial 2: significantly less total lost productivity with sumatriptan/naproxen, 27%, vs naproxen (<math>P=0.016</math>), placebo (<math>P&lt;0.001</math>) and sumatriptan (<math>P=0.002</math>).</p> <p>24 hour post-dose PPMQ:<br/>Trial 1: overall satisfaction with effectiveness in the sumatriptan/naproxen group, 50% vs 41%, 35% and 21% in the sumatriptan, naproxen and placebo groups (<math>P</math> values not reported).</p> <p>Trial 2: overall satisfaction with effectiveness in the sumatriptan/naproxen group, 53%, vs 42%, 35% and 19% with the sumatriptan, naproxen and placebo groups (<math>P</math> values not reported).</p> <p>Secondary:<br/>Not reported.</p> |
| <p>Silberstein et al<sup>68</sup></p> <p>Combination sumatriptan 85 mg/ naproxen sodium 500 mg 1 tablet administered at onset of migraine while pain</p>  | <p>DB, MC, PC, PG, RCT</p> <p>Men and women 18 to 65 years old with a 6 month</p>   | <p>Trial 1<br/>N=658</p> <p>Trial 2<br/>N=647</p>   | <p>Primary:<br/>2 hour pain free response</p> <p>Secondary:<br/>0.5, 1 and 4 hour pain</p>  | <p>Primary:<br/>2 hour pain free response:<br/>Trial 1: sumatriptan/naproxen significantly more effective than placebo, 52% vs 17% (<math>P&lt;0.001</math>).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective than</p>   |

| Study and Drug Regimen   | Study Design and Demographics   | Sample Size and Study Duration | End Points  | Results   |
|--|---|--------------------------------|---|---|
| was mild not more than 1 hour after onset<br><br>vs<br><br>placebo | history of migraine with or without aura and an average of 2 to 6 attacks per month in 3 months prior to study onset. | Single attack administration   | free response, sustained pain free response, 2 and 4 hour migraine free response, use of rescue medication within 24 hour post dose, 2 and 4 hour nausea, photophobia, phonophobia, 2 and 4 hour neck pain/discomfort and sinus pain/pressure | <p>placebo, 51% vs 15% (<math>P&lt;0.001</math>).</p> <p>Secondary:<br/>0.5, 1 and 4 hour pain free response:<br/>Trial 1: sumatriptan/naproxen significantly more effective vs placebo. Percent of patients pain free at 0.5 hours, 5% vs. 2% (<math>P=0.016</math>). At 1 hour, 20% vs 7% (<math>P&lt;0.001</math>). At 4 hours, 70% vs 25% (<math>P&lt;0.001</math>).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective vs placebo. Percent of patients pain free at 0.5 hours, 6% vs 2% (<math>P=0.021</math>). At 1 hour, 24% vs 7% (<math>P&lt;0.001</math>). At 4 hours, 67% vs 25% (<math>P&lt;0.001</math>).</p> <p>Sustained pain free response:<br/>Trial 1: significantly greater with sumatriptan/naproxen vs placebo, 45% vs 12% (<math>P&lt;0.001</math>).</p> <p>Trial 2: significantly greater with sumatriptan/naproxen vs placebo, 40% vs 14% (<math>P&lt;0.001</math>).</p> <p>2 and 4 hour migraine free response:<br/>Trial 1: sumatriptan/naproxen significantly more effective than placebo, 45% and 63% vs 15% (<math>P</math> value not reported) and 24% (<math>P&lt;0.05</math>).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective than placebo, 46% and 64% vs 14% (<math>P</math> value not reported) and 25% (<math>P&lt;0.05</math>).</p> <p>Use of rescue medications within 24 hours post dose:<br/>Trial 1: significant difference between treatment groups, 20% in the sumatriptan/naproxen group vs 47% with placebo (<math>P&lt;0.001</math>).</p> <p>Trial 2: significant difference between treatment groups, 16% vs 45% (<math>P&lt;0.001</math>).</p> <p>2 and 4 hour nausea, photophobia and phonophobia:</p> |

| Study and Drug Regimen   | Study Design and Demographics  | Sample Size and Study Duration | End Points  | Results  |
|--|--|--------------------------------|---|--|
|  |  |                                |   | <p>Trial 1: significantly lower percentage of patients in sumatriptan/naproxen group vs placebo (<math>P=0.018</math>, <math>P&lt;0.001</math>, <math>P&lt;0.001</math>).</p> <p>Trial 2: significantly lower percentage of patients in sumatriptan/naproxen group vs placebo (<math>P&lt;0.001</math> for all measures).</p> <p>2 and 4 hour neck pain/discomfort and sinus pain/pressure:<br/>Trial 1: sumatriptan/naproxen significantly more effective vs placebo (<math>P&lt;0.001</math> for all measures).</p> <p>Trial 2: sumatriptan/naproxen significantly more effective vs placebo (<math>P&lt;0.001</math> for all measures).</p> |
| <p>Smith T et al<sup>69</sup></p> <p>Combination sumatriptan 85 mg/ naproxen sodium 500 mg 1 tablet administered at onset of moderate to severe migraine</p> | <p>Phase III, OL, MC</p> <p>Men and women 18 to 35 years old with first migraine attack before 50 years, with an average of 2 to 8 moderate to severe attacks per month in 6 months prior to study onset</p> | <p>N=600</p> <p>12 months</p>  | <p>Primary:<br/>Pain severity, change from baseline in PPMQ scores, change from baseline in MSQ scores</p> <p>Secondary:<br/>Not reported</p> | <p>Primary:<br/>A total of 81% of all attacks were reported pain free at 2 hours post dose. At 3 months, the percentage of satisfied or very satisfied patients increased on all 8 PPMQ items. At 12 months, PPMQ results remained high.</p> <p>Mean MSQ scores increased by 13 to 15 points at 3 months. 3 and 12 month MSQ scores were significantly improved from baseline (<math>P&lt;0.001</math>).</p> <p>Secondary:<br/>Not reported.</p>   |
| <p>Winner P, et al<sup>70</sup></p> <p>Combination sumatriptan 85 mg/naproxen sodium 500 mg 1 tablet administered at onset of acute migraine attack</p>      | <p>MC, OL</p> <p>Men and women 18 to 35 years old with first migraine attack before 50 years, with a 6 month history of migraine with or without aura, and an average of 2 to 8 severe attacks</p>           | <p>N=562</p> <p>12 months</p>  | <p>Primary:<br/>Clinical adverse events, clinical chemical analysis</p> <p>Secondary:<br/>Not reported</p>                                    | <p>Primary:<br/>For overall safety data, 66% of patients reported at least one treatment-emergent adverse event.</p> <p>A total of 41 of 565 patients withdrew from the study due to an adverse event, 36 of which were non-serious. Overall, 14 patients had one or more serious adverse event; none were fatal or life-threatening. All were judged unrelated to treatment except one case of acute coronary syndrome.</p> <p>Clinical chemical analysis observed at 12 months. Range of 0.3 to 1.7 decrease in hemoglobin levels; no patient reported symptoms of</p>   |

| Study and Drug Regimen   | Study Design and Demographics   | Sample Size and Study Duration | End Points   | Results  |
|--|---|--------------------------------|--|--|
|  | per month in 6 months prior to study onset  |                                |  | blood loss. Minimal increases in ALT levels in 9 patients; none greater than 2 times the ULN. Minimal increases in serum creatinine levels in 9 patients; none exceeded 1.2 times the ULN. Minimal increases in BUN in 7 patients; highest being 30 mg/dL (1.3xULN).<br><br>Secondary:<br>Not reported.  |
| <b>Menstrual Migraine</b>  |   |                                |  |  |
| Allais et al <sup>11</sup><br><br>Almotriptan 12.5 mg<br><br>vs<br><br>zolmitriptan 2.5 mg | DB, MC, PC, R, RETRO<br><br>Patients with 12-month history of migraine and 2-6 migraine attacks in each of the two months preceding the trial | N=255<br><br>24 hours          | Primary:<br>Pain relief (from severe or moderate to mild or no pain) at 0.5, 1, 1.5 and 2 hours; pain free at 0.5, 1, 1.5 and 2 hours; sustained pain free 2 hours with no recurrence and no rescue medication over 24 hours); recurrence within 24 hours of treatment; and level of functional impairment before intake and after 0.5, 1, 1.5 and 2 hours<br><br>Secondary:<br>Tolerability defined as the number of patients reporting adverse events within 24 hours after dosing | Primary:<br>In the intent-to-treat group, almotriptan did not differ significantly from zolmitriptan for any of the variables tested.<br><br>Two hours after dosing, 67.9% of the 136 women who took almotriptan and 68.6% of the women who took zolmitriptan ( $P=0.900$ ) had obtained pain relief.<br><br>Evolution of pain from "moderate/severe" to "mild/no pain" was also similar in both groups, 14.9% of almotriptan-treated women vs 11.9% of zolmitriptan-treated women had improved at 0.5 hours ( $P=0.477$ ).<br><br>A pain-free state at 2 hours was reported by 44.9% of women on almotriptan and 41.2% on zolmitriptan ( $P=0.554$ ); 24 hours after dosing 56.6% and 64.7% of patients, respectively, were pain free ( $P=0.187$ ).<br><br>Recurrences 2-24 hours post-dose were reported in 32.8% and 34.7% of patients respectively ( $P=0.833$ ).<br><br>Use of rescue medication 2-24 hours after dose was reported by 21.8% of almotriptan and 25.4% of zolmitriptan ( $P=0.499$ ).<br><br>A sustained pain-free response was reported by 29.3% of almotriptan patients and 27.1% of zolmitriptan patients ( $P=0.698$ ).<br><br>Secondary:<br>Adverse effects in the 24 hours post-dosing were reported in 19.8% |

| Study and Drug Regimen   | Study Design and Demographics  | Sample Size and Study Duration       | End Points  | Results  |
|--|--|--------------------------------------|---|--|
|  |  |                                      |   | of almotriptan group and 23.1% of zolmitriptan group; 13.2% and 17.6% ( $P=0.328$ ) respectively, were considered to be triptan-related.   |
| Silberstein et al <sup>72</sup><br><br>Frovatriptan 2.5 mg daily<br><br>vs<br><br>frovatriptan 2.5 mg twice daily<br><br>vs<br><br>placebo | DB, MC, PC, XO<br><br>Women migraineurs aged >18 years, >1-year history of migraine, and an attack frequency of at least 3 to 4 (perimenstrual period) | N=443<br><br>3 perimenstrual periods | Primary:<br>Efficacy of frovatriptan in menstrual migraine given for 6 days (2 days before menses) in comparison with placebo<br><br>Secondary:<br>Not reported     | Primary:<br>The incidence of menstrual migraine was 67% (n=468) in the placebo treated group compared with 52% (n=484; $P<0.0001$ ) and 41% (n=483; $P<0.0001$ ) in the frovatriptan 2.5 mg daily and twice daily groups, respectively.<br><br>Significant reductions in headache severity were observed in frovatriptan-treated patients ( $P<0.0001$ ).<br><br>Frovatriptan administered twice daily was more efficacious than once-daily administration ( $P<0.0001$ ).<br><br>Secondary:<br>Not reported |
| <b>Cluster Headache</b>  |  |                                      |   |  |
| Siow et al <sup>73</sup><br><br>Frovatriptan 2.5-5.0 mg daily for up to 3 weeks  | OL<br><br>Median age=43, cluster headache history 1-38 years   | N=17<br><br>3 weeks                  | Primary:<br>Headache occurrence in patients with episodic and chronic cluster headaches for preventative and transitional therapy<br><br>Secondary:<br>Not reported | Primary:<br>8 of 9 patients with episodic cluster headache reported at least 75% improvement, with 100% relief within 48 hours of treatment.<br><br>3 of 8 patients with chronic cluster headaches had complete relief.<br><br>No adverse events reported.<br><br>Secondary:<br>Not reported   |
| Gobel et al <sup>74</sup><br><br>Sumatriptan SC 6 mg   | MC, OL<br><br>Patients 18-65 years of age with a diagnosis of cluster headache or episodic cluster headache  | N=52<br><br>1 year                   | Primary:<br>Efficacy of therapy defined by freedom from pain within 15 minutes in more than 90% of attacks<br><br>Secondary:<br>Tolerability defined by             | Primary:<br>Therapy was successful in 88% of all attacks ( $P$ value not reported).<br><br>Freedom from pain within 15 minutes in more than 90% of attacks was reported by 42% of patients ( $P$ value not reported).<br><br>Secondary:<br>Adverse events were reported by 62% of patients ( $P$ value not reported).  |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration                             | End Points   | Results  |
|---|--|--|--|--|
|   |  |  | adverse effects reported by patients   |  |
| Ekbom et al <sup>75</sup><br><br>Sumatriptan 6 mg SC<br><br>vs<br><br>sumatriptan 12 mg SC<br><br>vs<br><br>placebo | DB, MC, PC, R, XO<br><br>Patients 18-65 years with a diagnosis of cluster headache or episodic cluster headache  | N=134<br><br>Single dose study                             | Primary:<br>Headache improvement to mild or no pain at 5, 10 and 15 minutes<br><br>Secondary:<br>Not reported  | Primary:<br>At 10 minutes, headache relief was reported by 25% (placebo), 49% (6 mg), and 63% (12 mg) of patients.<br><br>At 15 minutes headache relief was reported by 35% (placebo), 75% (6 mg), and 80% (12 mg; $P<0.001$ for all comparisons vs placebo).<br><br>$P$ was not significant for 6 mg vs 12 mg.<br><br>Secondary:<br>Not reported  |
| <b>Cardiovascular Safety</b>  |  |  |  |  |
| Elkind et al <sup>76</sup><br><br>Frovatriptan 2.5 mg QD<br><br>vs<br><br>placebo                                   | DB, MC, PC, PG, RCT<br><br>Men and women 18 years and older with a history of migraine with or without aura for longer than 1 year, with an attack frequency of 1-6 moderate or severe migraines per month | N=75<br><br>Single migraine attack (follow-up at 36 hours) | Primary:<br>Cardiovascular effects assessed by a 24-hour Holter monitor in patients administered frovatriptan 2.5 mg for the acute relief of migraine headache<br><br>Secondary:<br>Not reported | Primary:<br>Similar numbers of patients experienced ST segment changes indicative of ischemia on the 24-hour Holter monitor (11% frovatriptan-treated vs 13% placebo-treated).<br><br>All episodes of myocardial ischemia or arrhythmias were asymptomatic and did not result in hemodynamic compromise.<br><br>The incidence of arrhythmias was higher in the placebo-treated patients than frovatriptan group (11% vs 3%, respectively).<br><br>There were no differences in heart rate or diastolic or systolic blood pressure. The incidence of adverse events was similar in the frovatriptan treated and placebo-treated groups.<br><br>Secondary:<br>Not reported |
| Fleishaker et al <sup>77</sup><br><br>Almotriptan 12.5 mg<br><br>vs   | DB, R, SD, 3-way, XO<br><br>Patients with mild-to-moderate   | N=20<br><br>Single dose                                    | Primary:<br>Assess cardiovascular effects of almotriptan in patients with mild-to-moderate hypertension  | Primary:<br>Almotriptan produced a dose-related change in systolic blood pressure for both 4 and 12 hours post-dose. Mean changes from baseline from 0-4 hours were $1.59\pm3.88$ , $1.85\pm5.94$ , and $4.84\pm5.99$ mm Hg for systolic blood pressure and $1.38\pm6.95$ , $6.25\pm9.54$ , and  |

| Study and Drug Regimen                     | Study Design and Demographics          | Sample Size and Study Duration | End Points  | Results   |
|--|--|--------------------------------|---|---|
| almotriptan 25 mg<br><br>vs<br><br>placebo | hypertension controlled by medications |                                | controlled by antihypertensive medication<br><br>Secondary:<br>Assess relationship between plasma concentrations and cardiovascular effects in a population that is possibly sensitive to the vasoconstrictive properties of the 5-HT <sub>1</sub> agonists | 11.0±10.6 mm Hg for diastolic blood pressure for placebo, almotriptan 12.5 mg, almotriptan 25 mg, respectively.<br><br>Secondary:<br>Plasma concentrations of almotriptan increased in a dose-related manner. There were no statistically significant differences in dose-related pharmacokinetic parameters between doses, indicating that the pharmacokinetics of almotriptan were linear for the dosage range studied for patients with controlled hypertension. |

Drug regimen abbreviations: IN=intranasal, SC=subcutaneous

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational, PC=placebo-controlled, PG=parallel-group, SD=single dose, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover

Miscellaneous abbreviations: ALT=alanine transaminase, BUN=blood urea nitrogen, ECG=electrocardiogram, HR=hazard ratio, IHS=International Headache Society, MqoLQ=Migraine Quality of Life Questionnaire, MSQ=Migraine-Specific Quality of Life Questionnaire, NNH=number needed to harm, NNT=numbers needed to treat, ODT=orally disintegrating tablet, PAQ=Productivity Assessment Questionnaire, PPMQ=Patient Perception of Migraine Questionnaire, RB=relative benefit, RR=risk ratio, ULN=upper limit of normal

**Special Populations****Table 5. Special Populations**<sup>4-12</sup>

| Generic Name           | Population and Precaution  |   |  |                       |                                     |
|------------------------|--|---|--|-----------------------|-------------------------------------|
|                        | Elderly/<br>Children   | Renal<br>dysfunction  | Hepatic<br>dysfunction   | Pregnancy<br>Category | Excreted in<br>Breast Milk          |
| Single Entity Products |  |   |  |                       |                                     |
| Almotriptan            | Safety and effectiveness in pediatric patients have not been established.<br><br>Dose reduction not required in the elderly. | The max daily dose should not exceed 12.5 mg per 24 hours; and a starting dose of 6.25 mg should be used. | The kinetics have not been assessed in liver dysfunction.<br><br>The max daily dose should not exceed 12.5 mg per 24 hours; and a starting dose of 6.25 mg should be used. | C                     | Unknown in humans.                  |
| Eletriptan             | Safety and effectiveness in pediatric patients have not been established.<br><br>Dose reduction not required in the elderly. | No dosage adjustment required.  | No dose adjustment necessary in mild to moderate impairment; therapy should be avoided in severe impairment.   | C                     | Yes; excreted in human breast milk. |
| Frovatriptan           | Safety and effectiveness in pediatric patients have not been established.<br><br>Dose reduction not required in the elderly. | No dosage adjustment required.  | No dose adjustment necessary in mild to moderate impairment.   | C                     | Unknown in humans.                  |
| Naratriptan            | Safety and effectiveness in pediatric patients have not been established.<br><br>Use in the elderly is not recommended.      | Use is contraindicated with CrCl < 15 mL/min.   | Not studied in hepatic impairment.   | C                     | Unknown in humans.                  |
| Rizatriptan            | Safety and effectiveness in pediatric patients have not been established.<br><br>Dose reduction not required in the elderly. | No dosage adjustment required; extra caution should be used in hemodialysis.                              | No dose adjustment necessary in mild to moderate impairment.   | C                     | Unknown in humans.                  |
| Sumatriptan            | Safety and effectiveness in  | No dosage adjustment  | The max single dose should not   | C                     | Yes; excreted in                    |

| Generic Name               | Population and Precaution  |                                      |  |                       |  |
|----------------------------|--|--------------------------------------|--|-----------------------|--|
|                            | Elderly/<br>Children   | Renal<br>dysfunction                 | Hepatic<br>dysfunction                       | Pregnancy<br>Category | Excreted in<br>Breast Milk                                       |
|                            | pediatric patients have not been established.<br><br>Dose reduction not required in the elderly.                                   | required.                            | exceed 50 mg in liver disease.               |                       | human breast milk; avoid breast-feeding for 12 hours after dose. |
| Zolmitriptan               | Safety and effectiveness in pediatric patients have not been established.<br><br>Safety and efficacy not evaluated in the elderly. | No dosage adjustment required.       | Dose reduction recommended in liver disease. | C                     | Unknown in humans.   |
| <b>Combination Product</b> |  |                                      |  |                       |  |
| Sumatriptan/<br>naproxen   | Safety and effectiveness in pediatric patients have not been established.<br><br>Dose reduction not required in the elderly.       | Not recommended if CrCl < 30 mL/min. | Contraindicated in hepatic impairment.       | C                     | Yes; both agents are excreted in human breast milk.              |

**Adverse Drug Events****Table 6. Adverse Drug Events (%)**<sup>4-12,78</sup>

| Adverse Event(s)                 | Single Entity |            |              |             |             |                       |                         |                          |              | Combination              |
|----------------------------------|---------------|------------|--------------|-------------|-------------|-----------------------|-------------------------|--------------------------|--------------|--------------------------|
|                                  | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan Injection | Sumatriptan Nasal Spray | Sumatriptan Oral Tablets | Zolmitriptan | Sumatriptan/<br>naproxen |
| <b>Cardiovascular</b>            |               |            |              |             |             |                       |                         |                          |              |                          |
| Acute coronary syndrome          | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                       |
| Angina                           | -             | <1         | -            | -           | <1          | -                     | -                       | -                        | <1           | -                        |
| Arrhythmia                       | -             | <1         | -            | -           | <1          | <1                    | <1                      | <1                       | <1           | -                        |
| Atrial fibrillation              | -             | -          | -            | <1          | -           | <1                    | <1                      | <1                       | -            | -                        |
| Atrial flutter                   | -             | -          | -            | <1          | -           | -                     | -                       | -                        | -            | ≤1                       |
| Bradycardia                      | -             | -          | <1           | -           | <1          | -                     | -                       | -                        | -            | -                        |
| Chest tightness/pain             | -             | 1-4        | 2            | -           | 5           | 2-3                   | -                       | 1-2                      | 2-4          | 3                        |
| Congestive heart failure         | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                       |
| Coronary artery vasospasm        | <1            | -          | -            | <1          | -           | -                     | -                       | -                        | <1           | -                        |
| Cyanosis                         | -             | -          | -            | -           | -           | -                     | -                       | -                        | <1           | -                        |
| Electrocardiogram changes        | -             | -          | <1           | -           | -           | <1                    | <1                      | <1                       | -            | -                        |
| Flushing                         | -             | -          | 4            | -           | -           | -                     | -                       | -                        | -            | ≤1                       |
| Heart block                      | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                        |
| Hypertension                     | <1            | <1         | -            | -           | 1-10        | 1                     | -                       | 1                        | <1           | ≤1                       |
| Hypertensive crisis              | -             | -          | -            | -           | -           | -                     | -                       | -                        | <1           | -                        |
| Hypotension                      | -             | -          | -            | -           | -           | 1                     | -                       | 1                        | -            | -                        |
| Myocardial ischemia              | <1            | -          | -            | -           | <1          | <1                    | <1                      | <1                       | <1           | -                        |
| Myocardial infarction            | <1            | -          | -            | <1          | <1          | -                     | -                       | -                        | <1           | -                        |
| Myocarditis, viral               | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                       |
| Palpitation                      | -             | >1         | 1            | -           | 1-10        | -                     | -                       | 1                        | ≤2           | >1                       |
| Peripheral vascular disease      | -             | <1         | -            | -           | -           | -                     | -                       | -                        | -            | -                        |
| PR prolongation                  | -             | -          | -            | <1          | -           | -                     | -                       | -                        | -            | -                        |
| Premature ventricle contractions | -             | -          | -            | <1          | -           | -                     | -                       | -                        | -            | -                        |
| Prinzmetal angina                | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                        |
| Pulmonary embolism               | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                        |
| QTc prolongation                 | -             | -          | -            | <1          | -           | -                     | -                       | -                        | <1           | -                        |
| Tachycardia                      | <1            | <1         | <1           | -           | <1          | -                     | -                       | -                        | -            | ≤1                       |
| Thrombophlebitis                 | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                        |
| Thrombosis                       | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                        |
| Vasospasm                        | -             | <1         | -            | -           | -           | -                     | -                       | -                        | -            | -                        |

| Adverse Event(s)              | Single Entity |            |              |             |             |                       |                         |                          |              | Combination          |
|-------------------------------|---------------|------------|--------------|-------------|-------------|-----------------------|-------------------------|--------------------------|--------------|----------------------|
|                               | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan Injection | Sumatriptan Nasal Spray | Sumatriptan Oral Tablets | Zolmitriptan | Sumatriptan/naproxen |
| Ventricular extrasystoles     | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Ventricular failure, right    | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Ventricular fibrillation      | <1            | -          | -            | <1          | -           | -                     | -                       | -                        | -            | -                    |
| Ventricular tachycardia       | <1            | -          | -            | <1          | -           | -                     | -                       | -                        | -            | -                    |
| <b>Central Nervous System</b> |               |            |              |             |             |                       |                         |                          |              |                      |
| Abnormal dreams               | -             | <1         | -            | -           | -           | -                     | -                       | -                        | -            | -                    |
| Agitation                     | -             | <1         | <1           | -           | -           | <1                    | <1                      | <1                       | -            | -                    |
| Amnesia                       | -             | -          | <1           | -           | -           | 1                     | -                       | -                        | -            | -                    |
| Anxiety                       | -             | -          | 1            | -           | -           | 1                     | -                       | -                        | -            | ≤1                   |
| Aphasia                       | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Ataxia                        | -             | -          | -            | -           | -           | -                     | -                       | -                        | <1           | -                    |
| Attention disturbances        | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Back pain                     | -             | >1         | <1           | -           | -           | -                     | -                       | -                        | -            | -                    |
| Burning                       | -             | -          | -            | -           | -           | 7                     | -                       | 1                        | -            | ≤1                   |
| Cerebral ischemia             | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | <1           | -                    |
| Cerebrovascular accident      | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                    |
| Cold sensation                | -             | -          | -            | -           | -           | 1                     | -                       | -                        | -            | ≤1                   |
| Confusion                     | -             | <1         | <1           | -           | -           | -                     | -                       | -                        | -            | -                    |
| Convulsions                   | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                    |
| Depersonalization             | -             | <1         | <1           | -           | -           | -                     | -                       | -                        | -            | -                    |
| Depression                    | -             | <1         | <1           | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Disorientation                | -             | -          | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Dizziness                     | >1            | 3-7        | 8            | 1-10        | 1-10        | 12                    | 1-2                     | >1                       | 6-10         | 4                    |
| Drowsiness                    | -             | -          | -            | 1-10        | 1-10        | 3                     | -                       | >1                       | -            | -                    |
| Dysesthesia                   | -             | -          | 1            | -           | -           | -                     | -                       | -                        | -            | -                    |
| Emotional lability            | -             | <1         | <1           | -           | -           | -                     | -                       | -                        | -            | -                    |
| Euphoria                      | -             | <1         | <1           | -           | -           | -                     | -                       | -                        | -            | -                    |
| Fatigue                       | -             | -          | 5            | 1-10        | 13-30       | 1                     | -                       | 2-3                      | -            | ≥1                   |
| Feeling strange               | -             | -          | -            | -           | -           | 2                     | -                       | -                        | -            | -                    |
| Hallucination                 | -             | -          | -            | <1          | -           | <1                    | <1                      | <1                       | <1           | -                    |
| Headache                      | >1            | 3-4        | 4            | -           | -           | 2                     | <1                      | >1                       | <1           | -                    |
| Hearing loss                  | -             | -          | -            | -           | -           | -                     | -                       | 1                        | -            | -                    |
| Heaviness                     | -             | -          | -            | -           | -           | 7                     | -                       | -                        | -            | -                    |
| Hot/cold sensation            | -             | -          | 3            | -           | -           | -                     | -                       | -                        | -            | -                    |
| Hyperacusis                   | -             | -          | <1           | -           | -           | -                     | -                       | 1                        | -            | -                    |

| Adverse Event(s)                   | Single Entity |            |              |             |             |                          |                            |                             |              | Combination<br>Sumatriptan/<br>naproxen |
|------------------------------------|---------------|------------|--------------|-------------|-------------|--------------------------|----------------------------|-----------------------------|--------------|---|
|                                    | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan<br>Injection | Sumatriptan<br>Nasal Spray | Sumatriptan<br>Oral Tablets | Zolmitriptan |   |
| Hyperesthesia                      | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hyperkinesia                       | -             | <1         | -            | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hypertonia                         | -             | >1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hypoesthesia                       | -             | >1         | 1            | -           | -           | -                        | -                          | -                           | 1-2          | -                                       |
| Hypotonia                          | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Impaired concentration             | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Incoordination                     | -             | <1         | -            | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Insomnia                           | -             | <1         | 1            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Intracranial pressure<br>increased | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Mental impairment                  | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Nervousness                        | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Neuropathy                         | <1            | -          | -            | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Optic neuropathy                   | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Pain                               | -             | >1         | 1            | -           | -           | -                        | -                          | 1-2                         | 2-3          | -                                       |
| Paresthesia                        | 1             | 3-4        | 4            | 1-10        | -           | 14                       | <1                         | 3-5                         | 5-9          | 2                                       |
| Personality disorder               | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Psychomotor disorders              | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | ≤1                                      |
| Somnolence                         | >1            | 3-7        | -            | -           | -           | -                        | -                          | >1                          | 5-8          | 3                                       |
| Stupor                             | -             | <1         | -            | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Subarachnoid hemorrhage            | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Vertigo                            | <1            | >1         | <1           | -           | -           | -                        | -                          | <1-2                        | ≤2           | ≤1                                      |
| Warm/cold sensation                | -             | -          | -            | -           | -           | -                        | -                          | 2-3                         | 5-7          | -                                       |
| Warm/hot sensation                 | -             | -          | -            | -           | -           | 11                       | -                          | -                           | -            | >1                                      |
| Weakness                           | -             | 4-10       | -            | -           | -           | 5                        | -                          | -                           | 3-9          | ≥1                                      |
| <b>Dermatological</b>              |               |            |              |             |             |                          |                            |                             |              |   |
| Angioedema                         | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| Bullous eruption                   | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Cheilitis                          | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Flushing                           | -             | -          | -            | -           | 1-10        | 7                        | <1                         | <1                          | -            | -                                       |
| Itching                            | -             | <1         | <1           | -           | <1          | <1                       | <1                         | <1                          | -            | -                                       |
| Photosensitivity                   | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | <1           | -                                       |
| Pruritis                           | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Rash                               | <1            | <1         | -            | -           | -           | <1                       | <1                         | <1                          | <1           | ≤1                                      |
| Sweating                           | -             | >1         | 1            | -           | -           | 2                        | -                          | -                           | <3           | -                                       |

| Adverse Event(s)                             | Single Entity |            |              |             |             |                          |                            |                             |              | Combination<br>Sumatriptan/<br>naproxen |
|--|---------------|------------|--------------|-------------|-------------|--------------------------|----------------------------|-----------------------------|--------------|---|
|  | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan<br>Injection | Sumatriptan<br>Nasal Spray | Sumatriptan<br>Oral Tablets | Zolmitriptan |   |
| Toxic epidermal necrolysis                   | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| Urticaria                                    | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | ≤1                                      |
| Vasculitis                                   | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| <b>Endocrine and Metabolic</b>               |               |            |              |             |             |                          |                            |                             |              |   |
| Diabetes mellitus                            | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Edema  | -             | <1         | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Goiter                                       | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Growth hormone increase<br>(mild)            | -             | -          | -            | -           | 1-10        | -                        | -                          | -                           | -            | -                                       |
| Hot flashes                                  | -             | -          | <1           | -           | 1-10        | -                        | -                          | -                           | -            | -                                       |
| Hypocalcemia                                 | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hypoglycemia                                 | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Hypothyroidism                               | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Liver function tests abnormal<br>or elevated | -             | <1         | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Menstrual irregularity                       | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| TSH levels increased                         | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| <b>Gastrointestinal</b>                      |               |            |              |             |             |                          |                            |                             |              |   |
| Abdominal aortic aneurysm                    | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Abdominal distension                         | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Abdominal pain                               | -             | 1-2        | 1            | -           | 1-10        | 1                        | <1                         | <1                          | -            | ≥1                                      |
| Bad taste                                    | -             | -          | -            | -           | -           | -                        | 13-24                      | -                           | -            | -                                       |
| Biliary colic                                | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Colitis                                      | <1            | -          | -            | -           | -           | <1                       | <1                         | <1                          | <1           | ≤1                                      |
| Constipation                                 | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Diarrhea                                     | -             | <1         | 1            | -           | -           | <1                       | <1                         | 1                           | -            | ≤1                                      |
| Diverticulitis                               | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Dysgeusia                                    | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Dyspepsia                                    | -             | 1-2        | 2            | -           | -           | <1                       | <1                         | <1                          | 1-3          | 2                                       |
| Dysphagia                                    | -             | 1-2        | <1           | -           | -           | 1                        | <1                         | <1                          | <2           | ≤1                                      |
| Eructation                                   | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Flatulence                                   | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Gastric ulcer                                | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Gastritis                                    | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Gastroesophageal reflex                      | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |

| Adverse Event(s)         | Single Entity |            |              |             |             |                          |                            |                             |              | Combination<br>Sumatriptan/<br>naproxen |
|--------------------------|---------------|------------|--------------|-------------|-------------|--------------------------|----------------------------|-----------------------------|--------------|---|
|                          | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan<br>Injection | Sumatriptan<br>Nasal Spray | Sumatriptan<br>Oral Tablets | Zolmitriptan |   |
| Gastrointestinal pain    | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Hematemesis              | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Hiccup                   | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hypersalivation          | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hyposalivation           | -             | -          | 3            | -           | -           | -                        | -                          | >1                          | -            | -                                       |
| Intestinal obstruction   | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Irritable bowel syndrome | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Melena                   | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Nausea                   | 1-2           | 4-8        | -            | 1-10        | 1-10        | -                        | 11-13                      | >1                          | 4-9          | 3                                       |
| Pancreatitis             | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Peptic ulcer disease     | -             | -          | <1           | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Splenic infarction       | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Swallowing disorders     | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Taste alteration         | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Vomiting                 | 1-2           | -          | 1            | 1-10        | -           | -                        | 11-13                      | >1                          | -            | ≤1                                      |
| <b>Genitourinary</b>     |               |            |              |             |             |                          |                            |                             |              |   |
| Acute renal failure      | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Dysuria                  | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Hematuria                | -             | -          | -            | -           | -           | <1                       | <1                         | 1                           | -            | -                                       |
| Impotence                | -             | <1         | -            | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Micturition              | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Nephrolithiasis          | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Nocturia                 | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Polyuria                 | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Renal insufficiency      | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| <b>Hematologic</b>       |               |            |              |             |             |                          |                            |                             |              |   |
| Anemia                   | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Eosinophilia             | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Hemolytic anemia         | -             | -          | -            | -           | -           | <1                       | <1                         | 1                           | -            | -                                       |
| Pancytopenia             | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Purpura                  | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Thrombocytopenia         | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | <1           | -                                       |
| <b>Musculoskeletal</b>   |               |            |              |             |             |                          |                            |                             |              |   |
| Abnormal gait            | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Abnormal reflexes        | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |

| Adverse Event(s)                   | Single Entity |            |              |             |             |                          |                            |                             |              | Combination<br>Sumatriptan/<br>naproxen |
|------------------------------------|---------------|------------|--------------|-------------|-------------|--------------------------|----------------------------|-----------------------------|--------------|---|
|                                    | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan<br>Injection | Sumatriptan<br>Nasal Spray | Sumatriptan<br>Oral Tablets | Zolmitriptan |   |
| Arthralgia                         | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Arthrosis                          | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Asthenia                           | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Ataxia                             | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Back pain                          | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Bradykinesia                       | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| CPK increase                       | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Dystonias                          | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Facial palsy                       | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Involuntary muscle<br>contractions | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Joint ache                         | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Muscle cramps                      | -             | -          | <1           | -           | -           | 1                        | -                          | -                           | -            | -                                       |
| Muscle tightness                   | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | >1                                      |
| Muscle stiffness                   | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Muscle weakness                    | -             | -          | <1           | -           | -           | 1                        | -                          | -                           | -            | ≥1                                      |
| Myalgia                            | -             | <1         | <1           | -           | <1          | 2                        | -                          | 1                           | 1-2          | ≤1                                      |
| Myasthenia                         | -             | <1         | -            | -           | -           | -                        | -                          | -                           | <2           | -                                       |
| Numbness                           | -             | -          | -            | -           | -           | 5                        | -                          | 1                           | -            | -                                       |
| Rigors                             | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Skeletal pain                      | -             | -          | 3            | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Tremor                             | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Tetany                             | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| <b>Respiratory</b>                 |               |            |              |             |             |                          |                            |                             |              |   |
| Asthma                             | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Bronchospasm                       | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | <1           | -                                       |
| Dyspnea                            | -             | <1         | <1           | -           | 1-10        | -                        | -                          | 1                           | -            | ≤1                                      |
| Esophagitis                        | -             | <1         | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Hyperventilation                   | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Laryngitis                         | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Nasal disorder/ discomfort         | -             | -          | -            | -           | -           | 2                        | 2-4                        | -                           | -            | -                                       |
| Nasal inflammation                 | -             | -          | -            | -           | -           | -                        | -                          | 1                           | -            | -                                       |
| Nose/throat hemorrhage             | -             | -          | -            | -           | -           | <1                       | <1                         | 1                           | -            | -                                       |
| Pharyngitis                        | -             | >1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Pleurisy                           | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |

| Adverse Event(s)                  | Single Entity |            |              |             |             |                          |                            |                             |              | Combination<br>Sumatriptan/<br>naproxen |
|-----------------------------------|---------------|------------|--------------|-------------|-------------|--------------------------|----------------------------|-----------------------------|--------------|---|
|                                   | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan<br>Injection | Sumatriptan<br>Nasal Spray | Sumatriptan<br>Oral Tablets | Zolmitriptan |   |
| Rhinitis                          | -             | -          | 1            | -           | -           | -                        | -                          | 1                           | -            | -                                       |
| Sinusitis                         | -             | -          | 1            | -           | -           | -                        | -                          | 1                           | -            | -                                       |
| Throat discomfort                 | -             | -          | -            | -           | -           | 3                        | 1-2                        | -                           | -            | -                                       |
| Throat or neck pain/pressure      | -             | -          | -            | 1-10        | <1          | -                        | -                          | -                           | -            | -                                       |
| Upper respiratory<br>inflammation | -             | -          | -            | -           | -           | -                        | -                          | 1                           | -            | -                                       |
| Wheezing                          | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| <b>Other</b>                      |               |            |              |             |             |                          |                            |                             |              |   |
| Accommodation disorders           | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Allergic reaction                 | -             | <1         | -            | <1          | -           | <1                       | <1                         | 1                           | 1            | -                                       |
| Anaphylactoid reaction            | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | <1           | -                                       |
| Anaphylaxis                       | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | <1           | -                                       |
| Angioneurotic edema               | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Bruising                          | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Cataract                          | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Conjunctival hemorrhage           | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Conjunctivitis                    | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Cough                             | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Deafness                          | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Death                             | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Decreased appetite                | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Decreased mental activity         | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| Dental pain                       | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Dry mouth                         | -             | -          | -            | -           | <5          | -                        | -                          | -                           | -            | -                                       |
| Earache                           | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Ear hemorrhage                    | -             | -          | -            | -           | -           | -                        | -                          | 1                           | --           | -                                       |
| Epistaxis                         | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Eye pain                          | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Facial edema                      | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Fever                             | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Heaviness sensation               | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Hiccups                           | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Hyperhidrosis                     | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Infection (various)               | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Irritability                      | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |

| Adverse Event(s)                               | Single Entity |            |              |             |             |                          |                            |                             |              | Combination<br>Sumatriptan/<br>naproxen |
|--|---------------|------------|--------------|-------------|-------------|--------------------------|----------------------------|-----------------------------|--------------|---|
|  | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan<br>Injection | Sumatriptan<br>Nasal Spray | Sumatriptan<br>Oral Tablets | Zolmitriptan |   |
| Jittery  | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Lacrimation disorder                           | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Lethargy                                       | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Leukopenia                                     | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Lymphadenopathy                                | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Malaise  | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Miscarriage                                    | -             | -          | -            | -           | -           | -                        | -                          | -                           | <1           | -                                       |
| Motion sickness                                | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Mouth/tongue discomfort                        | -             | -          | -            | -           | -           | 5                        | -                          | -                           | -            | -                                       |
| Neck/throat/jaw<br>pain/tightness/<br>Pressure | -             | -          | -            | -           | -           | 2-5                      | -                          | 2-3                         | 4-10         | 3                                       |
| Neurological/<br>psychiatric abnormalities     | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| Numbness of tongue                             | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Optic neuropathy (ischemic)                    | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Oral mucosal blistering                        | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Oropharyngeal edema                            | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Pain at injection site                         | -             | -          | -            | -           | -           | 59                       | -                          | -                           | -            | -                                       |
| Peripheral edema                               | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Pressure sensation                             | -             | -          | -            | -           | -           | 7                        | -                          | 1-3                         | -            | -                                       |
| Raynaud's syndrome                             | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Sedation                                       | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Seizure  | -             | -          | -            | <1          | -           | -                        | -                          | -                           | -            | -                                       |
| Sensation changes                              | -             | -          | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Shock  | -             | <1         | -            | -           | -           | <1                       | <1                         | <1                          | -            | -                                       |
| Speech disorder                                | -             | <1         | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Stomatitis                                     | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | -                                       |
| Stroke   | -             | -          | -            | -           | <1          | -                        | -                          | -                           | -            | -                                       |
| Syncope  | <1            | -          | <1           | -           | <1          | <1                       | <1                         | 1                           | <1           | -                                       |
| Systemic lupus<br>erythematosus                | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Temperature intolerance                        | -             | -          | -            | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Thirst   | -             | -          | <1           | -           | -           | -                        | -                          | -                           | -            | ≤1                                      |
| Thrombophlebitis                               | -             | <1         | -            | -           | -           | -                        | -                          | -                           | -            | -                                       |

| Adverse Event(s)     | Single Entity |            |              |             |             |                       |                         |                          |              | Combination          |
|----------------------|---------------|------------|--------------|-------------|-------------|-----------------------|-------------------------|--------------------------|--------------|----------------------|
|                      | Almotriptan   | Eletriptan | Frovatriptan | Naratriptan | Rizatriptan | Sumatriptan Injection | Sumatriptan Nasal Spray | Sumatriptan Oral Tablets | Zolmitriptan | Sumatriptan/naproxen |
| Tightness feeling    | -             | -          | -            | -           | -           | 5                     | -                       | -                        | -            | -                    |
| Tinnitus             | -             | <1         | 1            | -           | <1          | -                     | -                       | 1                        | <1           | ≤1                   |
| Tongue edema         | -             | <1         | -            | -           | -           | -                     | -                       | -                        | -            | ≤1                   |
| Vision abnormalities | -             | <1         | 1            | -           | -           | 1                     | -                       | -                        | -            | ≤1                   |
| Vision loss          | -             | -          | -            | -           | -           | <1                    | <1                      | <1                       | -            | -                    |
| Xerostomia           | 1             | 2-4        | -            | -           | -           | <1                    | <1                      | <1                       | 3-5          | 2                    |

CPK=creatinine phosphokinase, TSH=thyrotropin stimulating hormone

✓ Percent not specified.

- Event not reported.

**Contraindications / Precautions**<sup>4-12</sup>

The use of 5-HT-1 receptor agonists should not be used for the treatment of hemiplegic or basilar migraine. These agents are also contraindicated in presence of a medical history or signs or symptoms of ischemic cardiac (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), cerebrovascular (strokes of any type as well as transient ischemic attacks), or peripheral vascular syndromes, including ischemic bowel disease. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. The use of 5-HT-1 agonists have also been reported to cause vasospastic reactions other than coronary artery vasospasm, so caution should be employed when initiating anti-migraine therapies in this subpopulation. Additionally, these agents should not be administered to patients with other significant underlying cardiovascular diseases or in patients with uncontrolled hypertension, since these agents may increase blood pressure. Administration of a 5-HT-1 agonist should not be used within 24 hours of treatment with another 5-HT-1 agonist, an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

**Warning for Treximet**<sup>®12</sup>**Increased Cardiovascular and Gastrointestinal Risks**

**Cardiovascular Risk:** Treximet<sup>®</sup> may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

**Gastrointestinal Risk:** Treximet<sup>®</sup> contains a nonsteroidal anti-inflammatory drug (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

**Drug Interactions****Table 7. Drug Interactions**<sup>79</sup>

| Generic Name  | Interacting Medication or Disease  | Potential Result  |
|---|--|---|
| Selective serotonin agonists (all)  | Citalopram, escitalopram, duloxetine, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine | A "serotonin syndrome," including central nervous system (CNS) irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur in some patients. Rapid accumulation of serotonin in the CNS may occur. If coadministration of these agents is indicated, start with low dosages and closely monitor the patient.  |
| Eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, sumatriptan/naproxen | Ergot alkaloids (dihydroergotamine, ergotamine)  | The risk of vasospastic reactions may be increased. Possibly additive vasospastic effects. Use of 5-HT <sub>1</sub> agonists within 24 hours of treatment with an ergot-containing medication is contraindicated.   |
| Almotriptan, eletriptan, sumatriptan/naproxen   | Azole antifungals/ CYP3A4 inhibitors (e.g., fluconazole, ketoconazole, itraconazole, voriconazole)             | Plasma concentrations of certain 5-HT <sub>1</sub> receptor agonists as well as naproxen may be elevated, increasing the pharmacologic and adverse effects. Inhibition of certain 5-HT <sub>1</sub> receptor agonists and first-pass metabolism (CYP3A4) or decreased renal clearance by certain azole antifungal agents is suspected. Eletriptan should not be taken within 72 hours of itraconazole or ketoconazole, and almotriptan should not be taken within 7 days of itraconazole or ketoconazole. |

| Generic Name  | Interacting Medication or Disease   | Potential Result  |
|---|---|---|
| Naratriptan, rizatriptan, sumatriptan, zolmitriptan, sumatriptan/naproxen | Sibutramine   | A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur. The serotonergic effects of these agents may be additive. Monitor the patient for adverse effects if concurrent use cannot be avoided.   |
| Rizatriptan, sumatriptan, zolmitriptan, sumatriptan/naproxen              | Monoamine oxidase inhibitors (MAOIs) (e.g., isocarboxazid, phenelzine, tranylcypromine) | Inhibition of metabolism via MAO, subtype-A. Use of certain 5-HT <sub>1</sub> agonists concomitantly with or within 2 weeks following the discontinuation of an MAOI is contraindicated. If it is necessary to use such agents together, naratriptan appears to be less likely to interact with MAOIs. A reduction in metabolism may increase sumatriptan levels by 7-fold and increase the risk of cardiac toxicity. |
| Rizatriptan   | Propranolol   | Rizatriptan plasma concentrations may be elevated, increasing the pharmacologic and adverse effects. Inhibition of rizatriptan metabolism (MAO, subtype-A) by propranolol is suspected.   |
| Sumatriptan/naproxen  | Anticoagulants (e.g., dalteparin, enoxaparin, heparin, warfarin)                        | Risk of hemorrhagic adverse reactions may be increased due to the naproxen component. Caution should be exercised when using anticoagulants and naproxen concurrently. Routine monitoring of prothrombin times (PT) and signs of bleeding, especially from the gastrointestinal tract should be employed.   |
| Sumatriptan/naproxen  | Bisphosphonates (e.g., alendronate, etidronate, pamidronate)                            | Bisphosphonates and naproxen may both synergistically increase the risk of gastrointestinal (GI) adverse reactions, especially gastric ulcers. Caution should be exercised with concurrent administration along with routine monitoring.  |
| Sumatriptan/naproxen  | Lithium   | Renal lithium clearance may be reduced by naproxen by up to 20%. When initiating or discontinuing non-steroidal anti-inflammatory drug (NSAID) therapy or if changes are made to the dose or frequency, lithium levels should be monitored every 4 to 5 days until stable and observe patients for clinical changes.  |
| Sumatriptan/naproxen  | Methotrexate  | Naproxen may contribute to reduced renal clearance and increased methotrexate toxicity. Coadministration of some NSAIDs with high-dose methotrexate has resulted in death from severe hematologic and GI toxicities. Renal function and methotrexate levels should be monitored.  |

### Dosage and Administration

Table 8. Dosing and Administration<sup>4-12</sup>

| Generic Name          | Adult Dose  | Pediatric Dose                                | Availability            |
|-----------------------|---|---|-------------------------|
| Single Entity Product |   |   |                         |
| Almotriptan           | Migraine, with or without aura:<br>Oral: initial, 6.25-12.5 mg, may | Safety and efficacy in children have not been | Oral tablet:<br>6.25 mg |

| Generic Name | Adult Dose  | Pediatric Dose   | Availability   |
|--------------|---|--|--|
|              | repeat after 2 hours; maximum 2 doses per 24 hours  | established.   | 12.5 mg  |
| Eletriptan   | <u>Migraine, acute treatment:</u><br>Oral: initial, 20-40 mg, may repeat after 2 hours if headache returns; maximum single dose, 40 mg; maximum daily dose, 80 mg   | Safety and efficacy in children have not been established. | Oral tablet:<br>20 mg<br>40 mg   |
| Frovatriptan | <u>Migraine:</u><br>Oral: initial, 2.5 mg, may repeat after 2 hours; maximum, 7.5 mg per 24 hours   | Safety and efficacy in children have not been established. | Oral tablet:<br>2.5 mg   |
| Naratriptan  | <u>Migraine, with or without aura, acute treatment:</u><br>Oral: initial, 1-2.5 mg, may repeat once after 4 hours; maximum, 5 mg per 24 hours   | Safety and efficacy in children have not been established. | Oral tablet:<br>1 mg<br>2.5 mg   |
| Rizatriptan  | <u>Migraine, with or without aura, acute treatment:</u><br>Oral: 5 to 10 mg, may repeat after 2 hours; maximum, 30 mg per 24 hours  | Safety and efficacy in children have not been established. | Oral tablet:<br>5 mg<br>10 mg<br><br>Oral tablet, disintegrating:<br>5 mg<br>10 mg   |
| Sumatriptan  | <u>Migraine:</u><br>Oral: initial, 25-100 mg, repeat after 2 hours if needed; maximum 200 mg per 24 hours<br><br>Subcutaneous: initial, 6 mg, repeat in 1 hour if needed; maximum 6 mg per dose and 12 mg per 24 hours; lower doses may be used if side effects are dose limiting<br><br>Nasal spray: initial, 5-20 mg, if headache returns may repeat dose once after 2 hours; maximum, 40 mg per 24 hours<br><br><u>Cluster headache:</u><br>Subcutaneous: initial, 6 mg, repeat in 1 hour if needed; maximum 6 mg per dose and 12 mg per 24 hours; lower doses may be used if side effects are dose limiting | Safety and efficacy in children have not been established. | Nasal spray:<br>5 mg<br>20 mg<br><br>Oral tablet:<br>25 mg<br>50 mg<br>100 mg<br><br>Subcutaneous injection:<br>4 mg/0.5 mL<br>6 mg/0.5 mL |
| Zolmitriptan | <u>Migraine, with or without aura, acute treatment:</u><br>Oral: initial, 2.5 mg (or lower), may repeat after 2 hours; maximum 10 mg per 24 hours   | Safety and efficacy in children have not been established. | Nasal spray:<br>5 mg<br><br>Oral tablet:<br>2.5 mg<br>5 mg   |

| Generic Name                | Adult Dose   | Pediatric Dose   | Availability   |
|-----------------------------|--|--|--|
|                             | Intranasal: initial, 5 mg into one nostril, may repeat after 2 hours; maximum 10 mg per 24 hours   |  | Oral tablet, disintegrating:<br>2.5 mg<br>5 mg               |
| <b>Combination Products</b> |  |  |  |
| Sumatriptan/<br>naproxen    | <u>Migraine, with or without aura, acute treatment:</u><br>Oral: 1 tablet (85 mg/500 mg), may repeat after 2 hours; maximum 2 tablets per 24 hours | Safety and efficacy in children have not been established. | Oral tablet:<br>85 mg sumatriptan/<br>500 mg naproxen sodium |

### Clinical Guidelines

**Table 9. Clinical Guidelines**

| Clinical Guideline  | Recommendation(s)*   |
|---|--|
| American Academy of Neurology:<br><b>Practice Parameter: Evidence-Based Guidelines for Migraine Headache</b> <sup>80</sup>  | <p><u>Acute migraine attacks, mild to moderate:</u></p> <ul style="list-style-type: none"> <li>First-line therapy consists of oral nonsteroidal anti-inflammatory drugs (NSAIDs). The NSAIDs that are rated evidence level grade A and judged to have the best scientific and clinical impression of effect are aspirin, ibuprofen, naproxen sodium, and the combination of the three agents, acetaminophen (APAP), aspirin (ASA), and caffeine.</li> </ul> <p><u>Acute migraine attacks, moderate to severe:</u></p> <ul style="list-style-type: none"> <li>Triptans (i.e., naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are effective and relatively safe for the acute treatment of migraine headaches and are an appropriate initial treatment choice in patients with moderate to severe migraine who have no contraindications for its use</li> <li>Initial treatment with any triptan is a reasonable choice for moderate to severe headaches or in migraine regardless of severity that has not resulted in adequate relief from the administration of nonspecific medication (e.g., NSAIDs, non-opiates, combination analgesics, etc.).</li> <li>Experts recommend limiting acute therapy to two headache days per week on a regular basis.</li> <li>Opiate analgesics, particularly butorphanol nasal spray or oral combinations such as APAP with codeine should only be used on a limited basis as rescue therapy.</li> <li>For treatment of status migrainosus, the therapy of choice in the emergency department (ED) should be intravenous (IV) dihydroergotamine (DHE) plus antiemetics. Intramuscular (IM) or IV prochlorperazine as needed should be chosen as the first-line antiemetic in the ED.</li> </ul> |
| American Academy of Neurology/Child Neurology Society:<br><b>Practice Parameter: Pharmacological Treatment of Migraine Headache in Children and Adolescents</b> <sup>81</sup> | <ul style="list-style-type: none"> <li>Ibuprofen should be considered as first-line therapy. Acetaminophen can also be used as an alternative option.</li> <li>Sumatriptan nasal spray may also be used when the above analgesics fail; there is no data to support or contest the use of oral triptans in this population and inadequate data to draw conclusions on the efficacy of subcutaneous sumatriptan.</li> </ul>   |

| Clinical Guideline   | Recommendation(s)*   |
|--|--|
| American Academy of Family Physicians (AAFP)/American College of Physicians-American Society of Internal Medicine (ACP-ASIM): <b>Guideline on the Management and Prevention of Migraines</b> <sup>82</sup> | <ul style="list-style-type: none"> <li>• Use NSAIDs as first-line therapy.</li> <li>• In patients whose migraines fail to respond to NSAIDs, use migraine-specific agents. Recommended agents include intranasal DHE, oral naratriptan, oral rizatriptan, SC or oral sumatriptan, and oral zolmitriptan.</li> <li>• Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea with an antiemetic.</li> <li>• Acute therapies should be limited to no more than two times per week to guard against medication-overuse headache (or drug-induced headache) per expert opinion.</li> </ul>  |
| US Headache Consortium: <b>Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting</b> <sup>83,84</sup>  | <ul style="list-style-type: none"> <li>• Use migraine-specific agents (triptans, DHE, ergotamine) in patients with severe migraine and in patients whose migraines respond poorly to NSAIDs or combination analgesics, such as aspirin-acetaminophen-caffeine.</li> <li>• Recommended medications, based on at least two double-blind, placebo-controlled trials and clinical impression of effect, include the following: oral acetaminophen-aspirin-caffeine; oral aspirin; intranasal butorphanol; SC, IM, IV or intranasal DHE; IV DHE plus an antiemetic; oral ibuprofen; oral naproxen sodium; oral naratriptan; IV prochlorperazine; oral rizatriptan; SC, intranasal, or oral sumatriptan; oral zolmitriptan.</li> <li>• Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.</li> <li>• Consider self-administered rescue medication (e.g., an opioid that a patient can use at home when other treatments have failed) for patients with severe migraine that do not respond well to other treatments.</li> <li>• When possible, limit acute therapy to two days per week.</li> </ul> |
| European Federation of Neurological Societies (EFNS) <b>Guideline on the Drug Treatment of Migraine—Report of an EFNS Task Force</b> <sup>85</sup>   | <p>Acute migraine attack:</p> <ul style="list-style-type: none"> <li>• First line agents for mild or moderate migraine attacks include: acetylsalicylic acid, ibuprofen, naproxen, diclofenac, paracetamol (acetaminophen), acetylsalicylic acid plus paracetamol plus caffeine.</li> <li>• 5-HT<sub>1</sub> receptor agonists are specific migraine medications and should not be administered in other headache disorders except cluster headache. Triptans are often effective in patients not responding to NSAID therapies.</li> <li>• The use of triptans should be restricted to maximum 10 days/month to avoid inducing drug overuse (“rebound”) headaches.</li> </ul>   |

### Conclusions

Migraine is a common disorder with a one year prevalence rate in the United States (U.S.) of approximately 13%.<sup>86</sup> Most migraine sufferers require pharmacologic treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line therapy by most organizations. The U.S. Headache Consortium recommends migraine specific agents such as the selective serotonin agonists for patients with severe migraine and in patients whose migraines respond poorly to NSAIDs or combination analgesics.<sup>83,84</sup> A non-oral medication is recommended for patients whose migraine presents early with nausea or vomiting as a significant component of the symptom complex. The Consortium does not give preference to one selective serotonin agonist over another.

All of the selective serotonin agonists are approved for the acute treatment of migraine attacks with or without aura. The subcutaneous formulation of sumatriptan is also indicated for cluster headaches. Rizatriptan and zolmitriptan are available as orally disintegrating tablets, which dissolve rapidly without

water. These products are not absorbed through the buccal mucosa so they have the same rate of absorption as the oral tablets.<sup>77</sup> Sumatriptan and zolmitriptan are also available as nasal formulations.

A meta-analysis of 53 clinical trials including over 24,000 patients concluded that all of the available oral selective serotonin agonists are effective and well tolerated. Almotriptan 12.5 mg, eletriptan 80 mg and rizatriptan 10 mg produced the most consistent success; however, eletriptan was not as tolerable as sumatriptan 100 mg.<sup>27</sup> Of note that this meta-analysis was published prior to the reformulation of sumatriptan tablets in January 2004.

Numerous clinical trials have been conducted comparing the safety and efficacy of the selective serotonin agonists to each other. The comparative studies only use patient-reported assessment systems to establish efficacy, a potential limitation since pain can be biased by age, gender, cultural, and other factors. Additionally, the 2-hour and 4-hour post-dose time period, which is commonly used, is arbitrary and may not be clinically meaningful. Still another significant shortcoming is that clinical trials have not been conducted based on stage and severity of migraine attacks in varying patient populations. Another limiting factor includes under-dosing of the comparator drug and/or the lack of enrollment of patients who have failed a comparator drug.

Of the head-to-head studies that do demonstrate statistically significant differences in headache response rates, the statistical difference tends to be less than 10%. The clinical consequence of the statistical difference tends to be less than 10% and thus the clinical significance of this small difference is not known. Although clinical trials have compared the selective serotonin agonists head-to-head, there is insufficient clinical evidence to conclude that one 5-HT<sub>1</sub> agonist is safer or more efficacious than another when administered at equivalent doses. All selective serotonin agonists have been determined to be safe, effective, and well tolerated with comparable side-effect profiles. While the selective serotonin agonists have different pharmacokinetic properties, in general, these differences have not resulted in significantly different clinical outcomes.

There is insufficient clinical evidence to conclude that one selective serotonin agonist is safer or more efficacious than another. Therefore, all products within the class reviewed are comparable to each other in terms of clinical outcomes. The availability of sumatriptan offers a clinically effective agent in a generic formulation in a variety of dosage forms, including tablets, subcutaneous injections, and nasal spray. The newest product, available as a fixed-dose combination of sumatriptan and naproxen was launched in April 2008 in anticipation of the generic availability of sumatriptan. The combination product has been shown to effectively manage migraine headaches in clinical trials; however a clear benefit of this agent over the concomitant administration of generic sumatriptan and naproxen sodium has not been established. Clinical trials comparing the combination product to the individual components have been evaluated; however clinical trials of Treximet<sup>®</sup> vs sumatriptan plus naproxen are lacking. Therefore, conclusions regarding direct comparisons and clinical efficacy outcomes are unable to be made.

### **Recommendations**

In recognition of the role of the 5-HT-1 receptor agonists as abortive therapy for patients with migraine headaches and that the safety and efficacy profiles are comparable among agents within the class, no changes are recommended to the current approval criteria.

Oral Axert<sup>®</sup>, Imitrex<sup>®</sup>, Maxalt<sup>®</sup> and Maxalt MLT<sup>®</sup> are preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Oral Amerge<sup>®</sup>, Frova<sup>®</sup>, Imitrex<sup>®</sup>, and Relpax<sup>®</sup> require prior authorization with the following approval criteria:

- The patient has had a documented side-effect, allergy or treatment failure to Axert<sup>®</sup>, Maxalt<sup>®</sup>, and Imitrex<sup>®</sup>.

Zomig<sup>®</sup> nasal spray requires prior authorization with the following approval criteria:

- The patient has had a documented side-effect, allergy or treatment failure with Imitrex<sup>®</sup> Nasal Spray.

Sumatriptan tablet, injection, or nasal spray requires prior authorization with the following approval criteria:

- The patient has had a documented intolerance to brand Imitrex<sup>®</sup>.

In addition, since there is a lack of clinical trial data demonstrating better clinical outcomes with the combination formulation compared to co-administration of the individual components as separate entities, no changes are recommended to the current Treximet<sup>®</sup> approval criteria:

- The patient had a documented side effect, allergy, or treatment failure with 2 preferred Triptans  
AND
- The patient is unable to take the individual components (sumatriptan and naproxen) separately

In recognition of the benefits of migraine prophylaxis, it is recommended that the following approval criteria addressing above the quantity limits requests be added:

- The patient is taking a medication for migraine prophylaxis  
AND
- If the patient has more than 15 headaches per month, the patient is being followed by a headache specialist, or a neurologist.

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